OVERSIGHT OF THE NATIONAL CANCER INSTITUTE, 1981

HEARINGS

BEFORE THE

SUBCOMMITTEE ON
INVESTIGATIONS AND GENERAL OVERSIGHT

OF THE

COMMITTEE ON
LABOR AND HUMAN RESOURCES
UNITED STATES SENATE

NINETY-SEVENTH CONGRESS

FIRST SESSION

ON

EXAMINATION ON DEFICIENCIES IN THE USE OF EXPERIMENTAL DRUGS ON CANCER PATIENTS

NOVEMBER 3 AND 6, 1981

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OVERSIGHT OF THE NATIONAL CANCER INSTITUTE, 1981

TUESDAY, NOVEMBER 3, 1981

U.S. SENATE,
COMMITTEE ON LABOR AND HUMAN RESOURCES,
SUBCOMMITTEE ON INVESTIGATIONS AND GENERAL OVERSIGHT,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10:06 a.m., in room 4232, Dirksen Senate Office Building, Senator Paula Hawkins (chairman of the subcommittee) presiding.

Present: Senators Hawkins and Kennedy.

Staff present: Jay Howell, chief counsel; James F. Michie, chief investigator; Terri Parker, counsel; Tim Jenkins, investigator, majority staff; and Walter Sheridan and Larry Horowitz, minority professional staff.

OPENING STATEMENT OF SENATOR HAWKINS

Senator **HAWKINS**. We will come to order, please.

Good morning. I am Senator Hawkins. Seated to my left is Senator Kennedy. We are here today to discuss a number of cancers, but not cancers of the lung, stomach, breast, or pancreas. We are here to examine cancers of inaction, confusion, indecision, frustration, delay, and failure to communicate.

These cancers have existed for years within the National Cancer Institute's drug development program and in the regulation of that program by the Food and Drug Administration. Fortunately, they are administrative in nature and treatable. Nevertheless, these administrative deficiencies are in need of attention and that is why we are here today.

Before proceeding further, I think it is important for us to reassure the thousands of cancer patients now in treatment in cancer centers and hospitals across the Nation that there is cause for hope and that they should continue to trust in the care of their doctors. Patients and their families must remain confident that physicians involved in NCI-sponsored chemotherapy research and treatment are dedicated first and foremost to saving lives.

I believe the NCI's drug development program is needed and must go forward, but with improved direction and administration.

On March 1, 1981, which was 7 months ago, when the subcommittee initiated this investigation, our purposes were and continue to be fourfold: First, to identify program deficiencies and problem areas; second, to make them known to program managers and directors; third, to put these deficiencies and problems in proper perspective; and fourth, to encourage and effect their correction.

With regard to the NCI's drug development program, I believe the evidence gathered shows without question that there are serious weaknesses in the NCI's capability to monitor the hundreds of clinical trials in which thousands of patients are administered these drugs. The evidence further shows that there is indeed a need for increased monitoring.

In April of last year, the Chief of the NCI's Investigational New Drug Branch warned his superior of the "lack of compliance with FDA regulations in the misuse of NCI investigational drugs." In May of this year, the new Chief of that same branch at NCI warned, "I find it difficult to assure that FDA regulations as well as scientific priorities can be fulfilled."

In April of this year, the NCI learned that one of its principal physician-investigators at a federally funded comprehensive cancer center had conducted a clinical trial without a protocol, which is the medical term for a method of treatment. This protocol had not been approved by the NCI.

What did the NCI do about this? The NCI wrote a letter to the physician telling him not to do it again, and then instructed the physician to, in effect, investigate himself by reviewing all of his other protocols "to assure that they had been filed with and approved by the NCI."

The physician's registration with the NCI as a clinical investigator was suspended for just 1 month. Three weeks later, a contractor-monitor for the NCI visited the same cancer center and spoke with the physician whose license had been suspended. In his report to the NCI, the monitor stated, "The physician quite clearly did not like my raising the subject of compliance with the Federal regulations and stated that he, the physician, had no time for the FDA."

Earlier, in the spring of 1980, the NCI had information that another illegitimate clinical trial had been conducted at this very same cancer center. What did the NCI do about it? As far as can be determined, virtually nothing.

On June 16, 1981, the NCI reported to the FDA that an unapproved clinical study, involving six patients, had been conducted with a radio labeled drug meant for study in animals only. How did the NCI learn of this? Only by sheer chance. An NCI monitor had read about the clinical study in a medical journal and happened to recall that there had been no approval from the NCI or the FDA for the study of this drug in humans.

The NCI was moved to action on this one. The subcommittee was informed that there would be a site visit. Several days prior to the 1-day site visit by a 10-member NCI team, my subcommittee staff person requested a copy of any existing documents containing instructions for, and the responsibilities of, the site visit team. An NCI official responded that there was "nothing in writing; it is all verbal." A subsequent written request from me was required before we were successful in eliciting from the NCI the charter of the site visit team.

In late July of this year, the FDA inspected a laboratory at a comprehensive cancer center. The laboratory conducts preclinical studies with mice, rats, and dogs—studies designed to determine whether new drugs can and should be tested in humans.

The purpose of the FDA inspection was to ascertain whether this laboratory was abiding by regulations requiring good laboratory practices. The inspection revealed that there were 15 deficiencies in the operation of this laboratory; among them: no quality assurance unit, lack of written standard operating procedures, and uncleanliness. Earlier inspections at this same institution had revealed similar problems.

According to the FDA report, the scientist in charge stated to the inspectors that, "Nothing negative would come of this inspection," since the center has operated this way and nothing negative occurred after the last two inspections. The report further states that the scientist asserted that, "He did not care about the good laboratory practices and that he was only afraid if this report was requested by the press." On October 23, 1981, the FDA issued a notice of adverse findings to the cancer center requesting that the deficiencies be corrected.

[The following information was received for the record:]

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

TO : Associate Director, CTEP

DATE: April 30, 1980

FROM : Chief, Investigational Drug Branch, CTEP

SUBJECT: Lack of Compliance with FDA regulations in the misuse of NCI investigational agents

I am asking permission and your assistance in making it widely known that use of our investigational agents in protocol studies which have not been approved by DCT before they are begun will result in serious action by NCI: Clinical Contracts held by the institution at which the study is performed will be canceled, and those investigators who have conducted the study will be disqualified as registered investigators with the NCI.

I am aware of several studies with AMSA (AMSA + cis platinum at Cancer Center #1, and high dose AMSA with marrow rescue and AMSA + peptichemico Cancer Center #2) and have a report that somewhere a combination study with DHAD is ongoing. None of these studies have been sent to NCI before they were begun. There are many others like this.

There has been perhaps reasonable criticism of NCI in the past as representing a major delay in the initiation of clinical trials. This is not the case now. Furthermore our not responding to the misuse of our drugs offers investigators the option of avoiding review by NCI.

I dislike suggesting the above course of action but I believe that I cannot ask our NCI staff to do the jobs of both meeting FDA regulations and of insuring the safe and coordinated development of our new agents while allowing this misuse of investigational agents to continue.

Vincent H Bono Jr
Vincent H. Bono, Jr., M.D.

cc: Dr. Penta
Dr. Hoth

Principal Physician-Investigator
Comprehensive Cancer Center

April 25, 1981

Dear Doctor:

It has recently come to the attention of the National Cancer Institute that the Cancer Center has instituted a trial of the combination of two anticancer drugs . There is no approved protocol on file with the NCI for this study, which is required since one of the drugs is supplied to your institution under the IND held by the NCI.

This situation is unacceptable. It is impossible for the NCI to facilitate research on investigational agents when such research is conducted without our knowledge. The Code of Federal Regulations regarding responsiblities of the sponsor of an IND clearly states that research on investigational agents must be conducted within the framework of a protocol approved by the sponsor of an IND and on file with the FDA.

Although we hope that this is an isolated instance, the NCI will require the the following actions prior to your continuing research on investigational agents supplied to you by the Institute.

1) You review all protocols involving agents supplied to you under NCI IND's to assure that these protocols have been filed with and are approved by the NCI. In the interim, until this list is received and verified by the NCI, your investigator registration (FD-1573) with NCI is suspended.

2) You terminate any currently active protocols utilizing investigational agents supplied by NCI which are not on file with and approved by the NCI.

3) You immediately discontinue your study with the drug , and return all stocks of that drug to the NCI.

The seriousness of this situation should not be underestimated. A major mission of the National Cancer Institute is to facilitate the process of development of new chemotherapeutic agents. There are mutual responsibilities involved. The NCI takes the responsibility to provide investigational agents for research by clinicians. Investigators privileged to study these agents have the responsibility to meet the reasonable requirements of the NCI, which are based on an agreement between FDA and NCI governing the DCT Drug Development Program. If this agreement is jeopardized, this program of chemotherapeutic development may be halted.

We ask for your prompt attention to this matter.

Sincerely,

Cancer Therapy Evaluation Program
Division of Cancer Treatment, NCI

ANNUAL SITE VISIT REPORT

INVESTIGATOR: Dr. #1, Principal Physician-Investigator
LOCATION: Comprehensive Cancer Center
DATE: May 13, 1981
MONITOR: Contractor Monitor (for NCI)

On May 13, 1981 I visited the Comprehensive Cancer Center to conduct an annual site visit on the Adult Cancer Treatment Evaluation Program protocols, sponsored by NCI. These protocols are: number one, two and three , and # four . Protocol # five has recently been activated also, but no patients have yet been entered.

I met with Dr. #2 , an internist with responsibility for the Data Management Office. It appears that, although a clinician, he has acted as prime organizer and expander of the Data Management System used in the developmental therapeutic clinic. He noted that they had recently expanded this activity into the Gastro-intestinal Clinic. It will be in this clinic that protocol # five may be started. He noted that the Cancer Center is an institution which is sadly lacking in computer services, with only lab data being readily available in automated fashion. He has recently instituted links with Epidemiology and hopes to expand this to include all registration and demographic data for patients on study protocols. He understood that there were problems in collecting data on protocol #three and # six , but felt that he was unable to help in any way, as these studies are being conducted in a site remote from his Data Management System. It appears that Dr. #3 supervises these studies with the aid of a research nurse and his Data Management Office does not receive any detailed raw data, except for simple registration information. I told him that I would later discuss this matter with Dr. #1.

I then talked with person , who is head of the Data Management Office, supervised by Dr. #2 . We reviewed the monitor's reports and she stated that she found these extremely helpful and would like to see them available on a regular basis. I left the 4/30/81 report with her. I asked her about the system for obtaining interim counts obtained by patients from their own physician. She recognizes that this is a problem but they do have,ongoing,attempts to remedy or improve this deficiency.

I visited the pharmacy and met with pharmacist , the pharmacist responsible for investigational and new drugs. In response to my enquiry she noted that a new procedure had recently been instituted, whereby the pharmacy maintains a list of NCI approved protocols and their number. Each physician prescribing an investigational new drug for an NCI approved study is required to write the protocol number beside his signature, otherwise the prescription will not be honored. Lists are maintained on the data sheets, also, of authorized prescribers. Monthly reviews of all prescriptions for investigational drugs are carried out and a mechanism is available for follow-up of unauthorized signatures. In the first instance the pharmacy forwards a letter to the principal investigator, asking if the unauthorized signature had been authorized by the principal investigator to prescribe drug or medication. If the answer by the principal investigator was in the negative, a letter of reprimand is issued to the department head, supervising the unauthorized prescriber. There is not specifically a central inventory or Dispensing Log. There is, however, a record kept of all investigational new drug prescriptions dispensed. Cross accounting for supplies on hand is also undertaken. It should be possible to reconcile these two record sets and arrive at a close although perhaps not perfect accounting for drug supplies used.

I then met with Dr. #4 , one of the principal investigators, intimately involved with drug study #one . Dr. #4 , on this occasion, was extremely pleasant and helpful, unlike my last visit where he was defensive and irritated by my questions. He noted that following conduct of the study , standard grading criteria had been adopted for toxicity and physicians were now required actively to grade such data. A copy of the criteria is attached. He also noted that new flowsheets with visit orientation had been issued and were in use in the Gastro-intestinal Clinic. He has moved from the Department of Developmental Therapeutics to the GI-Service, where he is continuing his interest in investigational drugs. He noted that there attempts to improve the data collection system, with cooperation from the Data Management Office supervised by Dr. #2 . He felt that attempts to obtain interim blood counts by pressure on the private physician supervising the outpatient treatment, would improve the quantity and quality of data available.

Finally, I interviewed #1 . In going over the checklist, it was evident that he understood the need for Institutional Review Committee approval and that copies of such approval were available. He noted that written informed consent was always obtained, but that the forms were kept in the patients' chart. He understood the need to follow the protocol in detail and shared his feeling that protocols were frequently overwritten. He observed that on the day following my visit, there was to be a meeting in which the standard structure of protocols was to be reviewed. He understands the need for the classification and prompt reporting of adverse experiences and the need to follow up on dropouts. He is familiar with regulations as they pertain to record keeping and record retention. Laboratory normal ranges have not changed in the last twelve months. He is aware of the need for test article accountability and felt that the pharmacy was discharging its responsibility in this regard. He was also aware of the need for the principal investigator to personally check data and observed that he would never knowingly allow anything dishonest to occur.

Discussion then focussed on the question of the lack of data supply for protocols #3 and #4 . It appears that 49 patients have been entered onto Protocol #3 and 17 patients onto #4 . He is adamant that he has an understanding with NCI that he will not be required to supply data on unfunded NCI studies, even where NCI supplies the investigational drug. He maintains that this agreement was recently reviewed with NCI Dr. in conversation and it is his understanding that this arrangement remains in force. He feels that unless NCI agrees to provide additional funds, he must maintain this posture. He quite clearly did not like my raising the subject of compliance with the federal regulations and stated that he had no time for the FDA. It does not seem at all likely that Dr. #1 will initiate data submission on these two protocols, without further action from NCI. If NCI is truly in agreement with Dr. #1 that they do not require data submission on NCI approved protocols on investigational drug supplied by NCI, where these studies are unfunded, then such studies should not be forwarded to the Clinical Trials Monitoring Service for monitoring and data collection. If, however, NCI is not truly in agreement with Dr. #1 in regard to his stance about data collection on these unfunded studies, then the approval of such studies and supply of investigational new drugs to this institution should be reviewed.

(signed by Contractor Monitor)

ORRIN G. HATCH, UTAH, CHAIRMAN

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United States Senate

COMMITTEE ON LABOR AND
HUMAN RESOURCES
SUBCOMMITTEE ON INVESTIGATIONS
AND GENERAL OVERSIGHT
WASHINGTON, D.C. 20510

July 8, 1981

Dr. Vincent T. DeVita, Jr.
Director
National Cancer Institute
Building 31, Room 11A52
Bethesda, MD 20205

Dear Dr. DeVita:

As Chairman of the Investigations and General Oversight Subcommittee, I am writing to request certain information concerning the National Cancer Institute's scheduled site visit to the M. D. Anderson Cancer Center in Houston, Texas, on July 13, 1981.

Specifically, I would very much appreciate your providing to me a list of the site visit participants; the purpose for the site visit; and a detailed schedule of the responsibilities of and charges to the site visit team. In addition, I am requesting that you provide to me photocopies of correspondence, memoranda, reports, and any other materials pertaining to the decision to conduct the site visit and the reasons and justification for the site visit. It would be most helpful to the Subcommittee if you could provide these materials by the end of the workday on July 9, 1981.

I am also requesting that you provide to me a report on the findings, conclusions and recommendations of the site visit team.

Thank you for your cooperation in this matter.

Sincerely,

Paula Hawkins
United States Senator

PH:clb

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

National Institutes of Health
Bethesda, Maryland 20205

JUL 9 1981

The Honorable Paula Hawkins
Chairman, Subcommittee on Investigations
and General Oversights
United States Senate
Washington, D.C. 20510

Dear Madam Chairman:

The following information relating to the July 13 National Cancer Institute site visit to the M.D. Anderson Hospital is supplied as requested in your letter of July 8.

A. Site visit team participants

Name	Organization
Dr. Saul Schepartz	DCT, NCI
Dr. John Driscoll	DCT, NCI
Dr. David Johns	DCT, NCI
Dr. Daniel Hoth	DCT, NCI
Mr. David Keefer	OAM, NCI
Dr. William Goldwater	OD, NIH
Mr. F. William Dommel	OD, NIH
Dr. Alan Sartorelli	Yale University
Dr. Lawrence Baker	Wayne State University

B. Purpose of the site visit

During 1978, the NCI supplied Dr. Ti Li Loo, Principal Investigator on NCI contract N01-CM8-7185, with an experimental compound, 5-methyltetrahydrohomofolate (MTHHF) for contract animal pharmacology studies. In mid-June, 1981, it was discovered that Dr. Loo had participated in a four-patient clinical pharmacology study of MTHHF during the summer of 1980. M.D. Anderson Hospital possessed no IND at the time the study was conducted. This study appears to be a clear violation of both FDA regulations and our NCI contractual agreement. The purpose of the site visit is twofold: (1) the determination of the facts relating to the MTHHF incident and (2) a general review of M.D. Anderson Hospital institutional procedures regarding the use of investigational anticancer drugs.

C. Responsibilities of the site visit team

1. The site visit team is charged with determining answers to the following questions:
    - a. Was harm done to any patient?
    - b. Why was MTHHF administered to humans without an FDA approved IND?
    - c. Was informed consent obtained?
    - d. Was the protocol used approved by an M.D. Anderson Hospital IRB and a Radiation Safety Committee?
    - e. Who among Dr. Loo's administrative superiors were aware of the MTHHF study?
    - f. Was this an isolated incident or has Dr. Loo participated in other unauthorized experiments?
    - g. Are M.D. Anderson Hospital institutional procedures, as currently practiced, adequate for investigational anticancer drugs?
    - h. What actions are being taken by the institution to insure such violations do not occur again?
2. The site visit team is charged with:
    - a. recommending the course of action to be taken by the NCI regarding contract personnel and future funding of contract N01-CM8-7185;
    - b. recommending changes in M.D. Anderson Hospital institutional procedures regarding investigational anticancer drugs; and
    - c. determining whether a more detailed investigation of M.D. Anderson Hospital patient and drug records pertaining to NCI-sponsored investigational drug studies is required.

D. Materials relating to the site visit

The following correspondence, memoranda, reports, and other material pertaining to the decision to conduct the site visit and the reasons and justification for the site visit are appended to this letter:

1. Letter, Dr. Loo to Dr. Johns (05/26/78)
2. Letter, Dr. Engle to Dr. Loo (06/07/78)
3. Letter, Dr. Loo to Dr. Johns and two pages from an April 1980 - January 1981 progress report (02/03/81)
4. Memo, Dr. Penta to Dr. Hoth (06/11/81)
5. Memo, Acting Associate Director, DTP, to Acting Director, DCT, and AACR abstract (06/15/81)
6. Letter, Dr. Driscoll to Dr. Loo (06/16/81)
7. Letter, Dr. Penta to the FDA (06/16/81)
8. Memo, Special Assistant for Clinical Affairs to Director, Office for Protection from Research Risk (06/17/81)
9. Memo, Dr. Penta to Dr. Johns (06/17/81)

10. Memo, Dr. Penta for the record (06/19/81)
11. Letter, Daniel F. Hoth to Dr. Charles A. Le Master (06/19/81)
12. Memo, Chief, LMCB to Acting Associate Director, DTP (06/22/81)
13. Memo, Director, NCI to Acting Director, DCT (06/23/81)
14. Letter, Charles A. LeMaistre to Daniel F. Hoth (06/23/81)
15. Memo, Dr. Penta to Chief, LMCB (06/24/81)
16. Memo, Acting Associate Director, DTP, to Acting Director, DCT (06/24/81) with attached memo from Chief, LMCB, to Acting Associate Director, DTP (06/24/81)
17. Memo, Director OPRR to Associate Director for Extramural Research and Training (06/24/81)
18. Memo, Associate Director for Extramural Research and Training to Special Assistant for Clinical Affairs (06/24/81)
19. Memo, Acting Associate Director, DTP, to Acting Director, DCT (06/25/81)
20. Memo, Chief, LMCB for the record with five attachments (06/26/81)
21. Letter, Charles R. McCarthy to Robert C. Hickey (06/29/81)
22. Letter, Clyde Williams to Dr. Robert C. Hickey (07/02/81)
23. Paper presented at a September 1980, M.D. Anderson Hospital symposium
24. Background information package to be given to site visit team.

I will be happy to provide you with a report of the findings, conclusions and recommendations of the site visit team as soon as it is available.

Sincerely yours,

Vincent T. DeVita

Vincent T. DeVita, Jr., M.D.
Director
National Cancer Institute

May 26, 1981

Chief, Investigational Drug Branch, CTEP

Immediate Personnel Requirements in the Investigational Drug Branch

Associate Director, Cancer Therapy Evaluation Program

In order for the IDB to continue to perform its mission the following pressing personnel problems need to be met:

A. Drug Monitor Staff - The Branch is currently functioning with two drug monitors. Because the IDB is responsible for the monitoring of over 100 IND's, I find it difficult to assure that FDA regulations as well as scientific priorities can be fulfilled. There is an urgent requirement to hire as soon as possible one additional drug monitor. Specifically, Dr. Louise Lev, a trained Medical Oncologist, a requirement for this position, is currently available and interested in taking this job. Dr. Lev has previous experience working in the IDB as a drug monitor and is a highly qualified individual who could assume responsibilities here as soon as the clearance could be obtained.

One of the two current drug monitors, Dr. Robert Levenson has recently submitted his resignation, and is expected to leave within four weeks. Therefore, in order to assure an uninterpreted performance of IDB monitoring duties, another person would be required. Dr. Juan Posada, who is also a board eligible oncologist, could be available within the next four to six weeks. Dr. Posada is highly qualified to assume this position and would be a valuable addition to the monitoring staff.

Note that the addition of these two individuals would simply maintain the IDB monitoring staff at three, which is the level it has had for several years. I believe this staff size to be the minimum required to perform our duties.

B. In the Drug Regulatory Affairs Section, the retirement of a key individual in January has made a critical reduction of the level of effort available for performance of drug distribution responsibilities of the IDB, in spite of the fact that the workload has increased 20%. Currently the IDB has an approved slot for a GS-3/4 individual to assist in this vital area. Because the function of this Section is to provide a timely and steady flow of cancer drugs for research, the reduction of personnel in this area has meant a burden upon existing staff above and beyond the call of duty. It is therefore essential that we fill this position.

Daniel F. Hoth, M.D.

7/81 7/22,23,28/81

Comprehensive Cancer Center

Inspection of the Comprehensive Cancer Center was made as part of the Fourth Quarter Bio-Research assignments. This inspection was conducted under the Good Laboratory Practices Regulations while following compliance program 7348.808. More specifically this was an inspection of IND-18,411 "Toxicological Studies of drug in Mice, Rats, and Dogs" and was conducted in the laboratory facilities of the scientist in charge.

The study was involved with the toxicity of single intravenous doses of drug in mice and rats and of repeated intravenous doses given at two week intervals in dogs. The study included a comparison of the toxicity of drug with that of the approved drug Cisplatin. Additionally pyrogen studies were performed on rabbits using metoclopramide which was used as an anti-emetic in dogs. Finally trimellitic acid which is a major contaminant of drug preparations was also examined.

Inspection scientist found that the drug is supplied by the manufacturer. the Cisplatin is supplied to the Cancer Center by the National Cancer Institute. Review of the records concerning the supplying of the animals found they were from approved sources. The animal storage rooms were examined and it was found that the Center is in the process of installing monitors to record and adjust the temperature and humidity of the animal rooms on a room by room basis. Currently the animal rooms temperatures are adjusted according to the buildings temperature and humidity is added at the air intake source.

Data for randomly selected animals was compared against the raw data contained in the laboratory notebooks and it was determined that all tests were performed, slides, blocks, and necropsy reports for selected organs all coincided.

The Hematology and Biochemistry Laboratories were also visited and were found to have SOP's for their instrumentation. Scientist's laboratory lacked written SOP s for the calibration of their instrumentation. All equipment checked appeared to be in good operating order.

At the conclusion of this inspection a List of Observations was presented to scienti reporting the following observations.

1. There was no written approved protocol developed prior to the undertaking of the drug study, that clearly indicates the methods for the conduct of the study.

2. There is no Quality Assurance Unit as defined by the GLP's.

3. There is no Standard Operating Procedure in writting setting forth non clinical laboratory study methods that are adequate to insure the quality and integrity of the data generated during the course of the study.

4. There is no SOP's for the maintenance and the calibration of the laboratory equipment.

5. There is no unique identification system for rodents placed on the study.

8/12/81

O + attach: , cc:

Cancer Center
(cont.)

6. There is no testing of the drug to assure that the test article corresponds to its labeled identity, strength, purity, and uniformity.

7. The animal care facilities are inadequate in that there is not an adequate separation of species or test systems.

8. Feed and water used for the animals is not analyzed periodically to ensure that contaminants are not present.

The following were observed in the Animal Care Facilities:

9. There is no isolation of incoming rodents prior to sending those animals to the investigators area.

10. The Standard Operating Procedures for handling animals do not include the isolation of rodents.

11. The Standard Operating Procedures for the Animal Care Facility lacks procedures for the handling of dead and moribund animals.

12. There is no written schedule of cleaning, feeding and care of laboratory animals.

13. For sterilized feed, water, and bedding the results of the B. stearothermophilus spore strips results are not maintained as part of the permanent record.

14. Roaches were observed in the cage washing area and in the animal feed room, on the bags of chow and the floor.

15. Rodent pellets, apparently old were observed on the floor of the animal feed storage room beneath the animal feed.

Initally scientist stated he would not discuss the observations but added that the study is discussed with his staff prior to the initiation of the study. Concerning the lack of a Quality Assurance Unit, scientist stated he has no plans to develop a QAU. Regarding the SOP's, scientist agreed there are none in writing but they are understood. Scientist stated that he could not run his facility if they were to adhere to the regulations and would not accept the Investigators critical appraisal due to limited research background, finally adding he did not care about the GLP's and that he was only afraid taht the press might request the E.I. under F.O.I.

*. The prior inspection conducted on July 17, 18, 19, 1979 of scientist lab found similar deviation from the GLP's as cited during the current inspection. Those similar deviations are referred to as above by number 1, 2, 3, 4, 5, 7, 14 and 15. Scientist responded to the List of Observations stating Cancer Center could not confirm to the GLP's because it would be counter productive for a research institute. A Notice of Adverse Finding Letter was proposed as a result of the last inspection, however, it was not approved by the Bureau of Biologics.

Cnacer Center

The first inspection of the facility made as part of the pilot program for GLP's was made in January 1977 and reported corresponding observations to the current inspection including points: 1, 2, 3, 5, 7, 8, 9, and 15. Scientist and their president, . did not feel that the GLP's should be or could be applied to a research facility and could not see how they adapt these regulations to their operations, nor would they wish to do so stating it would be counter productive. The report was classified VAI, but the B.O.B. changed the classification to NAI.

Follow-up: Based upon the continuing deviation from the Good Laboratory Practices and scientist attitude-that correction will not be instituted because nothing has happened after the past two inspection and expects nothing to happen after this inspection, FDA District is recommending notice of Adverse Findings Letter.

M-90 hrs.
A 90 hrs.

Date Submitted: 8/6/81
Date Endorsed: 8/10/81
Date Typed: 8/12/81

SUMMARY OF FINDINGS:

Inspection of the Comprehensive Cancer Center was made as part of the NYK-DO workplans and as part of the Fourth Quarter Bio-Research Assignments. This inspection was conducted under the Good Laboratory Practice Regulations while following compliance program 7348.808. More specifically this was an inspection of IND-18,411, "Toxicological Studies of drug in Mice, Rats, and Dogs" and was conducted in the laboratory facilities of the scientist in charge.

This study is concerned with the toxicity of single intravenous doses of (1,2-diaminocyclohexane) -4-carboxyphthalato-platinum (II) in mice and rats and of repeated intravenous doses given at two week intervals in dogs. This study included a comparison of the toxicity of with that of the approved drug Cisplatin (cis-dichlorodiammineplatinum (II)). Additionally pyrogen studies were performed on rabbits using metoclopramide which was supplied by [redacted] of [redacted] In this drug study metoclopramide was used as an anti-Emetic in dogs. Finally TMA (Trimellitic Acid) which is a major contaminant of DCCPP preparations was also examined. The TMA was supplied by [redacted] Chemical Co., [redacted]

The prior inspection of scientist' laboratory and the Comprehensive Cancer Center in conjunction with the GLP's was made in Ju'y 1979. During that inspection the following points were listed on an FD-483 and presented to scientist those points included a lack of/a Quality Assurance Unit, and SOPs. The animal care facilities were not sufficient enough to separate test systems and there was no limited access to the archives. There were no study protocols developed prior to starting the study, no written records kept of the maintenance calibration and/or standardization of test equipment, and no inventory for test substances. Recorded data did not indicate the individual entering the data or if it was reviewed. There was a lack of a unique identification system for rodents which require periodic removal from their cages. Feed, water, and bedding is not analyzed periodically to ensure that contaminants that might effect the results of the study, are not present. Old rodent excreta and possible gnawed material was observed in an area adjacent to the feed storage area.

Scientist responded to the List of Observations by stating that Cancer Center could not conform with the requirements of the GLP regulations since it would be counter-productive for a research institute such as the Cance Center The report was classified VAI and a Notice of Adverse Findings letter was proposed to the Bureau of Biologics but was not approved.

The first inspection of this facility was made in January 1977 as part of the GLP pilot program and at that time the above points were found with the exception of the dual signature on records. No FD-483 was presented to management at that time in keeping with the program and management responded to the observations stating that they could not see how they could conform to the GLP's. The report was classified VAI and an information letter was proposed. The Cancer Center did not receive an Information Letter and the classification was changed by the Bureau of Biologics to NAI.

Current inspection found the following deviations from the Good Laboratory Practices. These observations were listed on the FD-483 and presented to the scientist at the completion of the inspection. There was no written approved protocol developed prior to the undertaking of the drug study, that clearly indicates the methods for the conduct of the study. There is no Quality Assurance Unit as defined by the Good Laboratory Practices. There is no Standard Operating Procedures in writing setting forth the study methods that are adequate to insure the quality and integrity of the data generated during the course of the study, nor is there an SOP for the maintenance and the calibration of the laboratory equipment. There is no unique identification system for rodents placed on the study. No testing of the drug is performed to assure that the test article corresponds to its labeled identity, strength, purity and uniformity. The animal care facilities are inadequate in that there is not an adequate separation of species or test systems. Feed and water used for the animals is not analyzed periodically to insure that contaminants are not present. These observations were made in the Pharmacology Laboratory of which scientist is Director.

The following observations were made in the Animal Care facilities, representatives of which were not available for the discussion of the List of Observations, however these points were brought to their attention during the inspection. Inspection of the Animal Care Facilities found there to be no isolation of incoming rodents prior to sending these animals to the investigators study area, additionally the Standard Operating Procedures for the Animal Care Facility lacks procedures for the handling of dead and moribund animals. There was a lack of a written schedule of cleaning, feeding, and care of laboratory animals. For sterilized food, water, and bedding the results of B. Stearothermophilus spore strips results are not maintained as part of the permanent record. Roaches were observed in the cage washing area and in the animal feed room on the bags of chow and the floor. Finally apparently old rodent pellets were observed on the floor of the animal feed storage room beneath the animal feed.

ORGANIZATION AND PERSONNEL:

The organizational structure for the particular study is such that the scientist acts in the capacity of co-investigator with his colleague and as Study Director. During the course of the study a third individual was involved in the work, this person is a Medical Technologist. Scientist is a member of Comprehensive Cancer Center Center and Director of the Pathology Laboratory, his curriculum vitae is attached as Exhibit #3 along with his biographical sketch. Scientist's colleague is Chief of Autopsy Services and Attending Pathologist at the Center, Exhibit #4 represents his biographical sketch. The third individual is a trained medical technologist and has worked with scientist for 25 years.

In addition to scientist' duties he is also Chairman of the Investigational Drug Committee which is responsible for approving data submitted by Investigators prior to forwarding the information on to the Agency in support of an IND. Scientist stated that he has voting power on the committee and stated he approved the data of the drug study for submission to the Agency, attached as Exhibit #5 is a memo from scientist concerning the drug Study, the voting power of this group is on a majority basis.

Scientist stated that there is no Quality Assurance Unit at the Cancer Center and as Study Director he accepts overall responsibility for the study and the data developed. Scientist stated that he can approve his own work because he is an expert in his field and has an international reputation. Concerning the decision to undertake a particular study scientist stated that this is usually decided upon in an informal manner with his staff, no protocol is written before the study but rather in retrospect.

The organizational structure of the research group of scientist does not report to anyone in management at the Center. Scientist stated that there is no management at the Center that would oversee his work.

Scientist stated that there is no formalized training program to update employees engaged in the conduct of nonclinical laboratory studies.

Concerning the point on how the facility deals with employee health problems that may effect the quality or the integrity of the study, scientist stated that the individual would have a reassignment of duties within the Center. According to scientist the drug study which started in October 1978 and ended in April 1980 accounted for approximately 10% of his time while that the third person's involvement was approximately 50%. Scientist's colleague state that his involvement was less than 5%.The scientist and his colleague's CV appear as Exhibits 3 and 4 respectively.

QUALITY ASSURANCE UNIT:

The Master Schedule Sheet appears as Exhibit #15. Review of records and discussion with scientist found that there is no Quality Assurance Unit nor is there Standard Operating Procedures in writing setting forth the nonclinical laboratory study methods to insure quality and integrity of the study. scientist stated that he alone is responsible for the overall aspects of the study.

Scientist stated there is no study protocol developed prior to the start of the study. According to scientist, he feels confident that the knowledge at Cancer Center is sufficient to operate a study without a study protocol. Scientist stated that protocols are developed after the study and that to follow a study protocol developed ~~and~~ prior to a study is too confining because in this trial scientist adjusted the dose during the study. Scientist stated he is familiar with the GLP's in principal. At the completion of the study a protocol/study plan is developed to represent the work performed.

The final study report was developed which included the investigational study plan (Exhibit #6).

FACILITIES:

Attached as Exhibit #7 is a floor plan of the seventh floor. Those animal rooms used by scientist are rooms 731A and B used for monkey and dogs respectively and room 730 used for rats and mice.

Environmental controls are performed on the sterilization of feed, water, and bedding, however the results of the B. stearothermaphilus strips are not maintained as part of the permanent record. Rodac test plates are used and were observed in use in the cage washing area however the results are not made a part of the permanent record. The Clinical Veterinarian stated they would be made part of the record.

Cleaning procedures of the cages are done four days a week as follows: the cages enter by a conveyor belt into the cage washer, the cages are ringed, washed and rinsed two final times, water temperature is between 180° F to 190° F and the total time for a cage to pass through the cage washer is approximately five minutes. Water bottles for the animal cages are also washed using the above cycle and are then sterilized. The animal rooms are fogged with Pynethean and are washed on a regular basis with cloot soap. The cages containing monkeys and dogs are cleaned daily, mid sized cages twice per week and small cages are changed once per week.

In the animal rooms which scientist uses it was observed in room 730 to contain mice for two different studies by two investigators and the mice were not identified with any distinguishing physical marks in the event they became loose. The animal care facility was inadequate in that there was not adequate separation of species or test systems.

Pest control procedures are handled by personnel in the Animal Care Facilities who employ the services of [redacted] Record review found that this firm had visited on 7/15/81 and sprayed diazanon. Accord- to scientist's colleague : , Supervisor of the Animal Facilities, the rooms to be sprayed are chosen by himself.

Examination of the animal rooms used by scientist staff determined that overcrowding was not a problem. Currently the facility is operating on a summer schedule and according to scientist [redacted] animals are available for research during the academic year.

Currently the facility is instituting a complex monitoring system for temperature and humidity monitoring of the animal rooms. Included in the monitoring system is an alarm back-up in the event that there is a malfunction of the control system. Presently temperature is maintained by a general thermostat and humidity is added at the source of the air conditioning system for the entire building. The completion of the new monitoring system is anticipated to be completed in four months.

EQUIPMENT:

Inspection of the facilities found their general condition, cleanliness, and ease of maintenance of equipment to be adequate. However, roaches were noted in the cage washing area and animal feed room and rodent pellets were noted on the floor of the animal feed room. All equipment for all the laboratories inspected including Biochemistry, Hematology, and Pathology found the equipment to be in a convenient location to where the work is performed. All equipment was apparently in good working order.

Inspection of the above three laboratories in relation to their specific equipment found SOPs and/or operating manuals to be lacking in scientist's Pharmacology Lab, but were present in the Biochemistry and Hematology Laboratories. These SOPs included a maintenance schedule and log as well as standardization and calibration of the equipment. All analytical equipment was apparently in good working order.

The only analytical equipment used by the Pharmacology Laboratory during this study was a spectrophotometer which appeared to be in good operating order and adequate for the analysis needed. This Perkin Elmer Spectrophotometer is checked by representatives of Perkin Elmer and the Laboratory has a service contract for the instruments maintenance. The spectrophotometer was used primarily for the stability studies. Inspection of the Hematology Laboratory headed by Dr. found their equipment for blood counting to be adequate, the unit is also used for human blood counts. The SOP for the Opto ELT-8 used for blood counting was complete for maintanance. Inspection of the Biochemistry Laboratory which is headed by Dr. found this laboratory to have a complete set of SOPs for maintenance of equipment. The equipment used are atomic absorption, liquid scentilation counters, SMAC, and R I A analysis. These two laboratories do not interpret the results but rather forward the results to the cientist then both he and his colleague interpret the results. Record review did not uncover any equipment malfunctions during the study.

TESTING FACILITY OPERATIONS:

There was no written approved protocol developed prior to the undertaking of the drug study nor were there any SOPs in writing setting forth nonclinical laboratory study methods that are adequate to insure the quality and integrity of the data generated during the course of the study.

Scientist stated that to develop a protocol in writing prior to the initiation of the study would be too confining in that he was studying an unknown and as such the dosage was not yet known. Scientist stated that he and his staff are familiar with the GLPs in principal. There is no testing of the drug or reagents to assure that the test article corresponds to its labeled identity, strength, purity, and uniformity.

ANIMAL CARE:

Receiving and distribution of test animals is the responsibility of the Animal Care Facility whose director is a person acting on a temporary basis. While the Center is actively persuing a veterinarian for the position. This person is an administrator and not a veterinarian; he in turn reports to a Center vice president. Information concerning the handling of incoming animals was provided by the scientist's colleague , Supervisor of Animal Facilities and the Center's , Clinical Veterinarian. According to supervisor, an investigator completes a request form requesting a particular lab animal. Supervisor then orders the animals. Upon receipt of the laboratory animals the information from the shipping carton is transferred to a Center Animal Receiving Report (exhibit #8) copies of which go to the vet , the investigator, accounting, and supervisor's files. If the animals are to be shipped directly to the investigator upon receipt, the animals are sent to the investigator who completes the animal identification card (ex. #9) as in the case of scientist'work. If the animals are to be identified by the Animal Care Facility personnel the information appearing on the shipping label (exhibit #10) is transferred to the animal identification card (exhibit #9) which is attached to the animal cage. In the case of dogs, these animals arrive with a U.S.D.A. number which means the vendor is licensed. The dogs are supplied by [redacted] and the rabbits are supplied by [redacted] In the case of rodents the animals are received from [redacted] Supervisor stated they have never done an inspection of any of the vendors. The vet does receive quarterly reports from [redacted] concerning the health of the animals in stock and their availability and these are made part of the record and were reviewed to be adequate. The vet is involved with animal health surveillance and is called in to make a diagnosis on sick animals.

During this inspection it was determined that there is no isolation of the rodents/received. upon receipt due to the large volume of rodents The vet stated he selects a rodent for testing from each shipment and the information is entered into the computer where it is stored for reference. Those rodents that are handled by the Animal Care Facility are identified by ear clips and placed in cages.

In the case of scientist'study the mice are received in his lab unidentified, scientist stated he puts approximately five rodents in a cage without any identification.

Upon receipt of the laboratory animals if the animals are determined to be diseased they are returned to the vendor however some animals are sent directly to the investigator where they are put into animal rooms as mentioned above.

As previously mentioned there was no protocol developed prior to the initiation of this study but rather the protocol was developed in retrospect. Scientist stated that he has enough expertise to conduct non-clinical trials without a written protocol developed at the beginning of the study. Mice and rats are supplied by [redacted]

The dogs supplied from [redacted] were all USDA licensed and fully conditioned. None of the animals supplied to scientist labs are isolated by the Animal Care Facility but rather they are placed into the animal rooms in scientist'area where they are held approximately two weeks prior to beginning the study. Animals and strains of test animals are selected by the investigators. Scientist stated he keeps five to six mice per cage and the individual animals are not identified. Each cage is identified with the Animal Identification Card (exhibit #9). All treatment of the animals during the study is identified however there is no data for the review of pre-treatment therapy for the animals. The housing of animals in the study including the type of bedding [redacted], [redacted] cage size and number of animals caged is recorded for review.

Currently the Center is undergoing repairs to their environmental controls for the animal rooms which will monitor temperature and humidity on an individual room basis. During the period and at present the rooms are maintained around 70°F. and the humidity is entered at the air intake source at around 50% according to Supervisor. Air filters are changed by the engineering department every seven days for the primary filter and between two and three months for the secondary filter. Light/dark cycles are maintained for the rodents in room 730 as noted on exhibit #7. Animal cages are changed on a routine basis; large cages used to house monkeys and dogs are changed on a daily basis, medium sized cages are changed twice per week while the small cages used to house mice are changed once per week.

Incoming animals which are held by the Animal Care Facilities are identified by ear clips whereas those sent to the individual investigators are not identified upon receipt unless specifically requested by the investigator. In scientist'case he receives the animals unidentified and does not identify them upon receipt. The SOP's for the Animal Care Facility (ex. #11) lacks written procedures for the handling of dead or moribund animals. All necropsy work performed on the drug study was handled by Supervisor. Scientist stated he was present for each necropsy and vet would take notes during these procedures. Vet would also trim the tissues chosen by Supervisor and place them in fixative. These tissues are then sent to the Histopathology Laboratory where the tissues are imbedded and mounted on slides. The slides are read by Supervisor. Review of the slides found all tissues to be included that were required for the specific necropsy. Animals selected for mounting of all organs were those expected to have the most toxicity and would have been on the study for approximately 32 days. Various animals were selected for review (numbers 80-4-D and 80-1-D) and both were found to have complete sets of slides.

Exhibit #12 represents the necropsy reports for animal 80-4-D, these reports in turn were compared against the slides and the tissue blocks and it was determined that for all the tissue reported on exhibit #12, slides and tissue blocks existed. Tissue slides are stored in Supervisor's office while the tissue blocks are stored in scientist'lab. Lab books for the study also substantiate the tissues selected during various necropsies.

The records of one rat and one mouse were examined for the tests performed on them during the acute toxicity study. Both animals raw data corresponded to the data submitted.

TEST AND CONTROL ARTICLES:

The drug is manufactured and distributed by [redacted] located in [redacted] The drug is shipped directly to the scientist. The drug is being compared against the currently approved drug known as Cis Pt and which scientist receives from the Comprehensive Cancer Center and is supplied to the Center by the N.C.I. The drug is identified by lot numbers which are subsequently recorded into the laboratory note books where the amounts issued are also recorded by lot numbers. Reserve samples were found to be properly stored. There is no running inventory of the drug only the information contained in the laboratory book indicating the amount used.

Stability data was reviewed where the DCCPP was examined at 22°C and 37°C and compared with TMA (Trimellitic Acid). Various pH's were also examined where the Phosphate Buffer was at a pH of 6.2, 7.2 and 8.0. The drug was also examined in Sodium Bicarbonate at room temperature and at 4°C. The drug in Sodium Bicarbonate was found to be stable at 4°C but lacked stability at 22°C., room temperature for long periods of time, however up to six hours it was stable. It is the practice of scientist during this study to dilute the drug in solutions of Sodium Bicarbonate in sterile, pyrogen free 5% dextrose and inject the animals within ten minutes. Trimellitic Acid as mentioned above is a minor contaminant of the drug preparations which is produced during the breakdown of the drug platinum complex in aqueous systems.

The drug is a lyophilized powder which is diluted with the Sodium Bicarbonate and 5% dextrose solutions for injection. The drug is stored in a desicator under lock and key and is available only to the investigators and the vet.

Scientist does not maintain a running inventory of the study drug but rather the information is available by reviewing the laboratory note books for this study. Reserve samples are retained of the drug however each lot is used within six months. No retesting is done on the reserve samples after the study had been completed.

Pyrogen studies were performed using rabbits and the raw data was compared with the submitted data where it was determined that all values matched.

The TMA was supplied by the manufacturer, [redacted] Co. [redacted], [redacted] while the metoclopramide was supplied in sterile vials from the [redacted] and was used as an anti-emetic.

Protocol and Conduct of a Nonclinical Laboratory Study:

There was no written approved protocol developed prior to the undertaking of the drug Study that would indicate the methods for the conduct of the study. Scientist stated that to develop a study protocol prior to starting the study would be too confining in that adjustments in the dosage had to be made during the study. Scientist also stated that he and his staff have enough expertise to conduct a nonclinical study without a written protocol. Scientist developed the protocol after the study. Scientist also developed the procedures for this study. Scientist is the principal investigator and the study director and is responsible for the conduct of the study. Scientist stated he is familiar with the GLP's in principal only. The raw data includes all information requested by the protocol since the protocol was developed in retrpspect, the raw data did include the frequency of animal observations. The raw data records were not signed however the only individuals making entries into these books are scientist and the vet. Specimens are selected after being on the study for the required period of time for necropsys or observations; these periods are listed in the protocol.

Storage and Retrieval of Records:

The archives for this study are located in scientist's office. The only individuals that have access to these files are scientist, the Supervisor and the veternarian. . Material to be added to the archives would simply be added to the log books whereas data retrieval is only by the above three mentioned individuals. Randomly selected animals were reviewed for completeness concerning raw data, specimens, slides and finished data. For animals 80-4-D and 80-1-D all information corresponded to the raw data and all blocks and slides were available for review.

The final report including the study plan appears as exhibit #6.

Exhibit #13 represents a letter from the Agency concerning the progress of the drug study.

Master Schedule:

Attached as exhibit #14 are the terminated IND's that were investigated by scientist beginning in 1963. Exhibit #15 represents active IND's in which scientist had an active role and were submitted either to the Bureau of Drugs or Bureau of Biologics.

A second study was selected for review which had been submitted to the Agency in 1979 and involved scientist. This IND [redacted]ealt with 10-Deaza-aminopterin. This study was conducted in a similar manner to the drug study. All information appeared to be complete after a general review.

DISCUSSION WITH the scientist

Prior to the preparation and issuance of the List of Observations to the scienti d the supervisor, scientist stated that he realized there were deficiencies in the operation of the study with reference to the GLP's. Additionally scientist stated that research could not be conducted with the strict adherence to the Good Laboratory Practices, and further stated he "would not accept my critical appraisal" of his study since I have limited research background. Scientist added that he felt "nothing negative will come of this inspection" since the Center has operated this way and nothing negative occurred after the last two inspections. Scientist asked for a copy of the final report and I stated it could be requested under the Freedom of Information Act from the District. Scientist could not understand why he would have to request a copy of an inspection of his own facility. Scientist stated that if there is a problem he felt that the Center should have the opportunity to discuss any problem. I informed the scientist that he could respond to the List of Observations after issuance. Scientist stated that he was aware there was no Quality Assurance unit and that he would not set up a "sham" Quality Assurance unit since it would be easy to "fudge" information. Concerning my background and the study scientist stated it should be reviewed by his equals, stating that I may be familiar with the regulations and know how to perform inspections, but during past inspections the Investigators were accompanied by Bureau personnel.

At the conclusion of the inspection a List of Observations (exhibit #2) was presented to the scientist in charge.
Cancer Center, Director of the Pharmacology Laboratory and co-principal investigator of the drug Study. Upon issuance of the FD-483 scientist read the points and stated that he would not discuss the observations stating that there were only negative points listed on the form. I stated that these were my observations and that many of these points had been brought to his attention in the past two inspections stating that by now correction should have been made and that I was affording him the opportunity to respond. Scientist stated that he could not run his facility if they were to adhere to the regulations. Scientist stated that point one concerning the lack of a written approved protocol developed prior to the undertaking of the drug Study would give a reader the impression that they operated without a protocol. I stated that he did operate without a written protocol and the observation was specific. Scientist stated that he discussed the study with his staff. Concerning the lack of a Quality Assurance Unit scientist stated he has "no plans" to develop a Quality Assurance Unit. Regarding the lack of a Standard Operating Procedure in writing to insure the quality and integrity of the data, scientist stated its not in writing but is understood. Scientist stated he is concerned that other groups requesting this report under F.O.I. such as a newspaper or consumer action group would get the impression the Center is not doing their work.

I stated again that these points were issued to him twice before and had not been corrected. Scientist stated he did not care about the GLP's that he was only afraid if this report was requested by the press.

Scientist stated that nothing has happened in the past (alluding to the 1977, 1979 inspections) and assures nothing will happen in the future stating further that he tries to meet the objectives of the GLP's but knows he is not in compliance with the Good Laboratory Practices. Scientist stated he finds the issuance of the List of Observations listing only negative points as "highly distasteful". Scientist did not respond to points four through point 15 inclusive.

ATTACHMENTS

1. Notice of Inspection
2. List of Observations
3.
4.
5. Investigational Drug Committee memo
6. Final report
7. Floor Plan
8. Animal Receiving Report
9. Animal Identification Card
10. Shipping Label
11. S.O.P.'s for the Animal Care Facility
12. Necropsy Reports
13. Agency Correspondance
14. Terminated IND's
15. Active IND's - Master Schedule

Investigator/ FDA

TPH:jh

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administrat
Rockville MD 20857

OCT 23 1981

NOTICE OF ADVERSE FINDINGS

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Reply to the attention of

President
Cancer Center

Bioresearch Monitoring Staff
(HFC-30)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear

An inspection of your laboratory at was made during the period of July 22 - 28, 1981. During the inspection particular attention was given studies entitled "Toxicological Studies of DCCPP in Mice, Rats and Dogs." These studies have been submitted in support of safety by to IND 18,411. Studies in support of the IND 16,157 for 10 deaza-aminopterin were also examined.

The following is a listing of the major deviations from good laboratory practices (GLP) regulations (Title 21, Code of Federal Regulations, Part 58) that were observed:

Section	BRIEF DESCRIPTION
58.35	There was no Quality Assurance Unit (QAU) composed of one or more individuals who were independent of personnel engaged in the study.
58.81(c)	Laboratory manuals and standard operational procedures (SOP) were not readily available to laboratory personnel.
58.120(a)	The study did not have an approved written protocol that clearly indicated the objectives and all methods for the conduct of the study.

The above and other additional deficiencies observed during the inspection were discussed with and presented to Dr. laboratory director, on Form FD-483 (copy attached) at the conclusion of the inspection.

Many of the deficiencies listed in the FD 483 were also found in previous inspections of your laboratories in 1977 and in 1979. The Food and Drug Administration considers the cited deficiencies to be major deviations from acceptable nonclinical laboratory practice that could adversely affect the validity of studies done under such conditions.

The agency requires that all studies performed after June 20, 1979, and submitted to support marketing applications, be conducted in accordance with the GLP regulations. If you elect not to comply with GLP regulations by correcting the cited deficiencies, the agency will not accept any nonclinical studies conducted in your laboratory unless such studies have been validated by a third party using procedures that are acceptable to the agency.

Please advise us within thirty (30) days as to what action you have taken to correct the deficiencies noted.

Sincerely yours,

Associate Commissioner for
Regulatory Affairs

cc:
HFC-30(copy also for UCI; to be forwarded by Dr. Lepore)
HFC-1
HFC-2
HFA-224
HFO-520
HFD-150/
HFR-2150/
HFB-700/
BIMo Program Managers (7)
HFD-1,
HFD-180/1
R/D Typed:mk:9/15/81/Redraft:9/21/81/9/28/81
Final Typed:mk:10/5/81

District Classification: NAI
(a NAF letter was recommended)
Headquarters Classification: VAI

Sct
10/5/81

Senator HAWKINS. I believe that these examples show all too clearly that some of the NCI-sponsored clinicians and scientists do not want to be monitored. Further, I believe these examples emphasize the need for adequate monitoring of these NCI-funded facilities and clinical trials.

There are other examples of problems in the NCI's drug development program. These include the lack of adequate accountability in the use of NCI's drugs, a shortage of resources to adequately analyze the data and results of clinical trials to determine their effectiveness, and lengthy delays in the submission of data to the FDA. Last, but not least, the NCI does not even know the identities of all of its own clinical investigators.

As we will learn this morning, the FDA's Bureau of Drugs, regulator of the NCI drug program, also has its share of problems. The Bureau has only four medical officers assigned to review and evaluate the voluminous paperwork submissions from the NCI, as well as from commercial drug firms involved in the search for new anticancer drugs. The amount of paperwork is absolutely mind-boggling.

At the FDA, important matters pertaining to the safe clinical use of these drugs in clinics have either slipped through the cracks or have gone unattended for months. This morning, we are going to hear testimony on several such cases. We will hear of inconsistencies in the instructions and warnings from the FDA and the NCI to clinical investigators—inconsistencies involving potential life-threatening reactions to some of these drugs. We will establish that, while the FDA and the NCI are "sister agencies," these "sisters" have never gotten along very well.

Among our witnesses today are a group of cancer patients and their relatives. They will emphasize the need for the NCI's drug development program. Most of these patients were saved by anticancer drugs. However, several of these witnesses will point out the need for adequate, informed consent for patients who volunteer to participate in clinical trials of experimental drugs as well as the long-needed requirement that doctors sign an affidavit stating they understand the side effects of the anticancer drugs.

Before yielding to my distinguished colleague, Senator Kennedy, I want to say that I am encouraged by the effort of Department of Health and Human Services Secretary Schweiker to review and evaluate the NCI-FDA program. A special task force began looking into these matters several weeks ago and will report its findings to the Secretary and to this subcommittee some time in December. I am also encouraged by movement in both the NCI and the FDA to reassess their programs and to affect improvement and correction where needed.

I am certain that my colleagues on this subcommittee and everyone else concerned, join me in the hope and determination that these hearings will be constructive, so that the Department of Health and Human Services, the NCI, the FDA and the thousands of physicians and scientists dedicated to the fight against cancer can get on with the task of making the necessary adjustments and improvements in these programs so vital to us all.

Senator Kennedy?

Senator KENNEDY. Thank you, Madam Chairman.

No single word strikes as much fear in Americans as "cancer." On this very day all across this Nation, thousands of families are living the nightmare of learning that cancer has stricken a loved one. They will face difficult and painful decisions about uncertain courses of treatment.

In recent weeks, we have read of new attacks on our national effort to treat cancer and ultimately to conquer it. Given the intolerable nature of the affliction and the incredible toll it takes, certain questions are inevitable.

So many forms of cancer are terminal diseases with no known cures. Often, all we have are experimental efforts which can sometimes kill a patient before the cancer itself does. We are on the frontier of medicine where there are no assurances and no comfortable answers. It is essential to put the hard questions of cancer treatment in reasonable perspective and to separate the institutional problems from the policy ones.

The treatment of terminally ill individuals can and must follow ethical guidelines. It involves agonizing alternatives for a patient's family, and often indescribable pain for the patient. There are no standards to make such choices easy, but we must insist on standards of free and informed choice.

First, a patient must have the right to give or withhold consent on the basis of full disclosure about any proposed treatment. Second, all side effects of any therapy must be reported without delay to all doctors testing or applying that therapy.

But we should not pretend that this will resolve our dilemma, and we cannot know the full dangers of any treatment in advance. We cannot know what side effects we may have to inform the next patient about. We have to live with that uncertainty, for only in that way can we ever hope to delay or prevent cancer deaths.

There have been recent, well-publicized complaints about the experimental character of cancer treatment. Melvin and Edna Wilkins, whose son's plight was featured in a Washington Post series, wrote a letter to the editor which has not yet been published. In their letter they protested, and I quote, "The oversimplification of our son's case and the implication that he was nothing more than a 'guinea pig' in the war on cancer is, at best, absurd and, at worst, extremely distressing personally. The 'side effect' of his cancer was 'certain death'; the 'side effects' from experimental drugs 'might be' death."

The Wilkins' recall how their father "was diagnosed as having inoperable, nonradiatable, virulent, terminal cancer in 1981. But he is alive today after experimental drug treatments. Where are his feelings expressed and others like him?" That is the end of the quote from the letter. The Wilkins' son was not so fortunate; he became another childhood death from cancer. But his parents still believe the effort to save him was worthwhile and they wrote in their letter:

> The war on cancer, like any war, is made up of many battles. We know of no past war where the winning side did not lose some battles. Our son lost his battle, but we consider his life to have had more meaning because his experiences contributed to the knowledge available to those who must fight the next battle. Our decision certainly was not made to gain knowledge; it was made to try and save our son's life. But the fact remains that another child with circumstances like Chris' may not die in the future because of his experience and our decision to fight.

My heart goes out to the Wilkins family and to other families facing the terror of cancer. I know what they are feeling. I remember the near despair when I was told that my son had cancer. I remember the choice we made for an experimental treatment. I can never forget how hard the treatment was for Teddy and our family. He is alive and healthy today, and his story is repeated each day in different parts of our country.

Sometimes the ending will be happy and sometimes it will be tragic. There are proper criticisms of treatment procedures, and we must reassure patients that every possible precaution will be taken. But we cannot eliminate all the risk, uncertainty, and anguish. The war against cancer is not yet won and there are questions to be based, but we must raise them with sensitivity and responsibility so that we do not add to the terrible burden of worried families. And above all else, with the Wilkins family, we can make "the decision to fight the next battle."

I want to commend the chairman for holding these hearings; I know of her interest in the cancer program and her dedication to solve the problem that exists without weakening the many strengths that the program now has.

Senator **Hawkins**. Thank you, Senator Kennedy.

We do appreciate the sensitivity here. I imagine there is not a person in the audience who has not had cancer touch their family, and it is a dreaded word.

Senator Humphrey and Senator Nickles have asked that their prepared statement be entered into the record.

[The prepared statements of Senators Humphrey and Nickles follow:]

PREPARED STATEMENT OF SENATOR HUMPHREY

Madam Chairman: My congratulations to you for continuing to pursue the question of how well we are doing in our war on cancer. That war is primarily orchestrated by the National Cancer Institute, armed with an annual budget exceeding $1 billion. The American people have a right to know what is being accomplished with this money, and whether the work is being done in a careful and thoughtful manner.

As we both know, Madam Chariman, the Washington Post recently published a four-part series examining the activities of the National Cancer Institute and the physician/investigators supported by NCI grants. The series was extremely critical of NCI's performance. In my view, however, the series was less than balanced reporting. Nevertheless, it had some important messages to send: that our search for cancer treatment breakthroughs should not blind us to the needs and sufferings of those who are treated, and that all legal, ethical and scientific guidelines must be adhered to.

Unfortunately, the Post writers seemingly ignored the fact that cancer is a family of devastating diseases, frequently leading to disability and death. Furthermore, it is through careful research and quite a bit of luck that cancer treatment has progressed as far as it has. Because of the work that has been performed to date, many types of cancer can now be more promptly discoverd, and treatment (whether surgery, radiation or chemotherapy, or a combination of these) initiated at the earliest possible moment.

Still, no one would deny that chemotherapeutic agents have side effects, some quite serious. Nevertheless, even common drugs, such as aspirin, have side effects and should be avoided by certain individuals. The use of therapeutic agents is always one in which the benefits and risks must be assessed. Sometimes, initial hopes and impressions have proven faulty. After all, none of us, not even physicians, are infallible; however, we must do the best we can.

Madame Chairman, I am happy to see that you, with the cooperation of the distinguished Senator from Massachusetts, have called as witnesses cancer patients, their families, physician-investigators and several civil servants. Too frequently, we hear only from high-ranking administration spokes persons or from representatives of national associations. It is refreshing to hear from those people who are directly affected by the policies set by the Congess, including those government workers who must implement the laws we pass, and the programs we establish.

In summary, Madam Chairman, I hope that these hearings will lead to an improved attack on cancer and one that takes great care to protect the public health and safety. Lest there by any doubt, this hearing is NOT one looking for scapegoats, but is IS one looking for ways to improve our struggle against a frightening family of diseases.

PREPARED STATEMENT OF SENATOR NICKLES

Madam Chairman: I would like to call attention to the recent series of articles in the Washington Post which reported that the National Cancer Institute has failed to adequately monitor the use of potentially fatal anticancer drugs. The 1-year study by the Post documented 620 cases in which experimental drugs were implicated in the deaths of cancer patients. These deaths, the articles said, amount to only a fraction of the thousands of people who have died or suffered in cancer experiments in recent years.

I would like to cite an example of one such cancer patient, Jerry McClennan, whose case was documented in the October 20 issue of the Post. McClennan became part of a phase I study, an experiment whose main purpose, the Post discerned, was "not to treat the cancer, but to observe the side effects of the drug and to establish the proper dose to be used in further tests." McClennan, at that time, understood none of these purposes and endured the terrible painful side effects of the experimental drug in hopes that his cancer might be cured. Three weeks ago, on the morning of September 30, Jerry McClennan died at Miami Veterans' Administration Hospital.

If allegations are correct, I am incensed at such insensitive experimentation with human life. The National Cancer Institute must provide an effective program for monitoring the use of experimental anticancer drugs.

I would like to commend Senator Hawkins for her scheduling of oversight hearings on this matter in the Senate Labor and Human Resources Investigations Subcommittee.

Due to increased scientific discovery and understanding, triumph over cancer seems closer today than ever before. On the eve of success, the fight against cancer must not be diminished but strengthened. Yet, the Federal Government cannot continue to pour billions of dollars into the National Cancer Institute without adequately insuring that funds are used for effective scientific research and in the best interests of cancer patients.

I urge my colleagues to join me in watching with great care the progression of these investigations.

Senator **HAWKINS**. For our first panel of witnesses today, we have with us a group of individuals—patients and parents of patients—who are quite familiar with experimental chemotherapy. There were quite a few of them; we have divided them into two groups to accommodate the room here today.

I believe all of our witnesses today are of the opinion that the NCI's anticancer drug development program is needed and should go forward. I think we should restate that. We are all of the opinion that this program is needed and should go forward.

My colleagues on this subcommittee are most grateful to the family members and patients who have come here today to share with us their experiences. I would like to welcome you, and first introduce Mr. and Mrs. Paul Agostino of Medford, Mass. Mr. Agostino is a retired police officer and his wife is a former nurse. The Agostinos' 9-year-old son, Kevin, underwent surgery for a brain tumor in 1974 and had chemotherapy until 1976.

To their right are Mr. and Mrs. Donald Palmadessa of Ridgefield, N.J. The Palmadessas lost their 14-year-old son to cancer in 1977.

May I say that we are most appreciative of your willingness to be with us here today. I would like to begin first with the Palmadessas.

Mr. Palmadessa, your son underwent chemotherapy with two drugs, as I understand it—BCNU and methyl CCNU—from 1973 to 1976, and he died of kidney failure in 1977. Is that accurate?

STATEMENT OF MR. AND MRS. PAUL AGOSTINO, MEDFORD, MASS.; AND MR. AND MRS. DONALD PALMADESSA, RIDGEFIELD, N.J.

Mr. **Palmadessa**. Yes.

Senator **Hawkins**. Prior to his treatment, can you tell us what your doctors told you about possible adverse reactions?

Mr. **Palmadessa**. They told us there would be side effects, but not kidney problems. They told us there would be nausea; they were checking his liver, but no kidney problems.

Senator **Hawkins**. You were never given any information regarding possible damage, then, to your son's kidneys?

Mr. **Palmadessa**. No.

Senator **Hawkins**. Mrs. Palmadessa, after your son became fatally ill with kidney failure, what did your doctors tell you regarding the cause?

Mrs. **Palmadessa**. He said that something toxic caused the kidney failure, but not the chemotherapy.

Senator **Hawkins**. Not the chemotherapy, but some toxic agent, possibly?

Mrs. **Palmadessa**. Yes.

Senator **Hawkins**. Now, as I understand it, Mr. Palmadessa, you wrote a letter to the FDA in April of this year. Would you tell us what prompted you to write that letter and what you were seeking from the FDA?

Mr. **Palmadessa**. I read an article in the Washington Post that they found children with brain tumors that were still being treated with drugs that caused kidney failure. Well, they were all related to my son's problem, and I just wanted the FDA to find out more information on it and if the kidney failure was related to the chemotherapy in my case.

Senator **Hawkins**. Did they respond to your letter?

Mr. **Palmadessa**. Yes.

Senator **Hawkins**. How long did it take?

Mr. **Palmadessa**. About 2 months.

Senator **Hawkins**. Two months?

Mr. **Palmadessa**. Yes.

Senator **Hawkins**. We have provided you with a copy of that letter. Do you have that?

Mr. **Palmadessa**. Yes.

Senator **Hawkins**. Would you read it aloud, please?

Mr. **Palmadessa**. "Dear Mr. Palmadessa, your letter of April 7, 1981 concerning the use of methyl CCNU in treating your son from January 1973 to May of 1976 has been forwarded by the New York District Office to this office for reply.

"MethylCCNU was, at the time of your son's treatment and still is, considered an investigational new drug. We are enclosing a copy of the publication, 'Clinical Testing for Safe and Effective Drugs,' that explains the procedures that must be followed when using an investigational drug.

"If you have specific questions, please contact this office. Sincerely yours."

Senator **Hawkins**. Is the attachment that you have to yours the same as I have here, "Clinical Testing for Safe and Effective Drugs?"

Mr. **Palmadessa**. Yes, right.

Senator **Hawkins**. How do you feel about this response that you got from FDA? Do you understand it?

Mr. **Palmadessa**. No; it tells me nothing. I did not finish reading it.

Senator **Hawkins**. You did not even finish reading all of these printed pages with the pictures of how to treat, et cetera?

Mr. **Palmadessa**. No.

[The following information was received for the record:]

Donald Palmadessa
695 Elm Avenue
Ridgefield, NJ 07657

April 7, 1981

Food & Drug Administration
850 3rd Avenue and 30th Street
Brooklyn, New York 11232

Dear Sir:

My name is Donald Palmadessa and I reside at 695 Elm Avenue, Ridgefield, New Jersey 07657. I am writing this letter to get further information on an article that appeared in the Washington Post on or about April 2, 1981. It appeared in The Record (April 2, 1981 - page A15) under the subtitle "Testing of Cancer Drug Faulted".

My son Michael Palmadessa was stricken in 1972 with a malignant brain tumor (Astro Cytoma). After an operation on January 16, 1973, he was given Methyl CCNU from January 1973 to May 1976. We (my wife and I) were not advised that this drug could cause kidney failure.

Why was this drug put out without further testing of this nature? We believe it was not fair and justified.

We are in support of the FDA continuing their research on this drug.

We would appreciate more information on the whole matter.

Sincerely yours,

Donald Palmadessa

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

June 17, 1981

Donald Palmadessa
695 Elm Avenue
Ridgefield, NJ 07657

Dear Mr. Palmadessa:

Your letter of April 7, 1981 concerning the use of methyl CCNU in treating your son from January 1973 to May 1976, has been forwarded by the New York District Office to this office for reply.

Methyl CCNU was, at the time of your son's treatment, and still is, considered an investigational new drug. We are enclosing a copy of the publication "Clinical Testing for Safe and Effective Drugs" that explains the procedures that must be followed when using an investigational drug.

If you have specific questions, please contact this office

Sincerely yours,

Consumer and Professional Relations Staff
Bureau of Drugs (HFD-5)

Enclosures

CLINICAL TESTING FOR SAFE AND EFFECTIVE DRUGS

INVESTIGATIONAL DRUG PROCEDURES

Before 1962, there was no requirement that the Food and Drug Administration be notified that drugs were being tested on humans.

The 1962 Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act greatly strengthened the Government's authority over clinical (human) testing of new drugs.

With this new regulatory authority, the Food and Drug Administration has taken steps to:

1. Provide added safeguards for those on whom drugs are tested.
2. Improve reports by drug investigators.
3. Establish investigative procedures to supply substantial scientific evidence that a drug is safe and effective.

First Steps

Before a new drug may be tested on humans, the sponsor (usually a pharmaceutical firm, sometimes a physician) must give the FDA the information specified as a "Notice of Claimed Investigational Exemption for a New Drug" (Forms FD 1571, 1572, and 1573), known as an "IND." Copies of these IND forms may be obtained from:

Document and Records Service Section
(HFD-106)
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

The IND should include the following information:

a) Complete composition of the drug, its source, and manufacturing data, to show that appropriate standards exist to insure safety.

b) Results of all preclinical investigations, including animal studies. Initially, these should be directed toward defining the drug's safety, rather than its efficacy. The data must demonstrate that there will not be unreasonable hazard in initiating studies in humans. Further animal studies may be conducted concurrently with clinical studies. The Bureau of Drugs will, on request, comment on the adequacy of the proposed animal studies. The FDA generally requires as a minimum: (i) pharmacological profile, (ii) acute toxicity be determined in several species of animals and that the route of administration be that which will be used in the animal trials, (iii) short term studies ranging from two weeks to three months depending upon the proposed use to evaluate toxicity. Additional animal studies are frequently necessary.

c) A detailed outline (protocol) of the planned investigation.

d) Information regarding training and experience of the investigators. (See "Qualifications of Investigators.") Investigators are responsible to the sponsor and are required to submit, to the sponsor (not the FDA), either Form FD 1572 for clinical pharmacology or Form FD 1573 for clinical trials.

e) Copies of all informational material supplied to each investigator. (The type of information is listed in Form FD 1571.)

f) An agreement from the sponsor to notify the FDA and all investigators if any adverse effects arise during either the animal or human tests.

g) The investigator's agreement to obtain the consent of the person on whom the drug is to be tested before the test is made.

h) Agreement to submit annual progress reports and commitments regarding disposal of the drug when studies are discontinued.

Physician-Sponsored IND

When an investigator wishes to act as sponsor for the use of a drug solely as a research tool or for early clinical investigation of a drug of therapeutic or diagnostic potential (clinical pharmacology—phases 1 and 2) a simpler abbreviated form of submission is acceptable. An example would be the study of a drug that no manufacturer is interested in sponsoring. An outline of such a study should provide the following information:

1. The identity of the compound or compounds, together with the facts that satisfy the investigator that the agent may be justifiably administered to man as intended.

2. The purpose of the use and the general protocol.
3. Appropriate background information, including a brief statement of the investigator's scientific training and experience and the nature of the facilities available to him.

The physician sponsoring this form of IND deals directly with the FDA. The FDA has no authority over the practice of medicine and cannot require a physician to prescribe or not to prescribe a drug for a particular illness. But physicians are encouraged to submit an IND when they use a drug for purposes other than those approved by the FDA, when the drug was marketed. This enables the FDA to accumulate data on the safety and efficacy of the drug for that kind of treatment and to share the information with other physicians.

The Clinical Investigation

The kind and extent of the investigational drug tests are crucial to producing the substantial scientific evidence of safety and effectiveness needed to approve the drug for marketing. This evidence is obtained in three phases:

Phase I

Pharmacology studies are used to determine toxicity, metabolism absorption and elimination, and other pharmacological actions; preferred route of administration, and safe dosage range. These studies involve a small number of persons and are conducted under carefully controlled circumstances by persons trained in clinical pharmacology.

Phase II

Initial trials are conducted on a limited number of patients for a specific disease treatment or prevention. Additional pharmacological studies performed concurrently on animals may be necessary to indicate safety.

Phase III

Proposals for this phase, involving extensive clinical trials, are in order if the information obtained in the first two phases demonstrates reasonable assurance of safety and effectiveness, or suggests that the drug may have a potential value outweighing possible hazards. The phase III studies are intended to assess the drug's safety, effectiveness and most desirable dosage in treating a specific disease in a large group of subjects. The studies should be carefully monitored, no matter how extensive.

The FDA receives constant reports on the progress of each phase. If the continuation of the studies appears to present an unwarranted hazard to the patients, the sponsor may be requested to modify or discontinue clinical testing until further preclinical work has been done.

30-Day Delay

After the sponsor submits his IND, he must wait 30 days before beginning clinical tests. This delay enables the FDA to review the protocol to make certain it contains all of the necessary information and to assure that patients are not exposed to unwarranted risks. The 30-day period may be extended if the FDA feels additional time is needed for the sponsor to correct deficiencies in the protocol. The FDA also may waive the delay requirement if it feels such action is justified.

Sponsors may discuss their protocols at any time either before or during the tests with the Office of Scientific Evaluation, Bureau of Drugs.

Tests in Institutions

Drug tests on persons in hospitals, prisons, research facilities, and other institutions must be carefully supervised by institutional review committees.

The committees must be composed of persons with varying backgrounds, such as lawyers, clergymen or laymen, as well as scientists. They are appointed by the institution involved in the study. The FDA inspects the institutions periodically to determine if the committees are operating properly.

Qualifications of Investigators

The sponsor of an investigational new drug (usually the manufacturer) will ask the clinical investigator to supply the following information on Form FD 1572 (for the clinical pharmacologist engaged in phase 1 or 2 trials) or Form FD 1573 (for the physician engaged in phase 3 clinical trials):

1. A statement of his education, training and experience.
2. Information regarding the hospital or other medical institution where the investigations will be conducted; special equipment and other facilities.

The training and experience needed will vary, depending upon the kind of drug and the nature of the investigation. In phase 1, the investigator must be able to evaluate human toxicology and pharmacology. In phase 2, the clinicians should be familiar with the conditions to be treated, the drugs used in these conditions and the methods of their evaluation. In phase 3, in addition to experienced clinical investigators, physicians not regarded as specialists in any particular field of medicine may serve as investigators. At this stage, a large number of patients may be treated by different physicians to get a broad background of experience.

Obligations of Investigators

The investigator must keep careful records of his study and retain them for at least two years after the NDA is approved. The records must be made available promptly to the drug sponsor and to the FDA when required. Regular progress reports must be sent to the sponsor.

Reports must be sent to the sponsor immediately when dangerous adverse effects are observed, so the FDA and the other investigators can be notified, and the study stopped if the hazard warrants.

The regulations regarding consent of human beings given investigational drugs must be observed.

Patient Consent

The law requires that before using investigational drugs on human beings, the physician must "obtain the consent of such human beings or their representatives except when it is not feasible or when in his professional judgment it is contrary to the best interest of such human beings."

The consent for use of an investigational new drug in phase 1 and phase 2 must be in writing. In phase 3, it is the responsibility of the investigator, taking into consideration the physical and mental state of the patient, to decide when it is necessary or preferable to obtain consent in other than written form.

If written consent is not obtained, the investigator must obtain oral consent except as provided above, and record that fact in the medical record of the person receiving the drug.

Causes for Termination of Investigation

The FDA may direct the sponsor to terminate an investigation at any stage under certain conditions. These include:

Evidence of significant hazard.
Convincing evidence that the drug is ineffective.
Submission of false data.
Omission of material information.
Unsatisfactory manufacturing practices.
Failure to conduct the investigation in accordance with the plan submitted by the sponsor and approved by the FDA.
Commercialization of the drug. The IND regulations are not intended to provide a way of marketing a drug for profit without an approved NDA.
Failure to submit progress reports at intervals not

exceeding one year.

Failure to report serious or potentially serious adverse reactions.

Failure to meet requirements for patient consent.

The Commissioner may notify the sponsor of any of the above conditions and invite immediate correction. A conference may be arranged. If the corrections are not effected immediately, the Commissioner may require the sponsor to terminate the investigation and recall unused supplies of the drug. The drug in question may not be reintroduced into clinical testing in man until additional data have been submitted to the FDA and the Commissioner has approved the proposed resumption of the study.

The Investigator and "Promotion"

The regulations forbid manufacturers or any persons acting for or on their behalf to disseminate any promotional material concerning a new drug prior to completion of the investigation.

This is not intended to restrict the full exchange of scientific findings in scientific or other communications media. Its purpose is to restrict promotional claims by the sponsor until the safety and effectiveness of the investigational drug have been established. Violation of the regulations by an investigator may result in FDA action to deny him further supplies of the drug. The manufacturer may also jeopardize his right to sponsor the investigation.

Special preclearance before Human Trials

Before starting an investigation in any of the following categories, FDA approval is required for:

a) Substances controlled under Schedule I of the Controlled Substances Act (PL 91-513).

b) Investigations of drugs so toxic that their use may be justified only under special conditions.

c) Substances proposed for treatment of drug dependence.

d) Reinstitution of drug investigations which had been terminated by the Commissioner.

Use of Drugs for Laboratory Procedures

New drugs used only for studies in vitro (test tubes) or in laboratory animals are exempted from the new-drug provisions of the Act provided they are labeled "Caution—Contains a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans."

The exemption does not apply, however, for a new drug used in vitro when this use will influence the diagnosis or treatment of disease in a human patient—for example, discs to determine the sensitivity to antibiotics of bacteria in culture, or a stick or strip of paper incorporating a reagent to test for sugar in the urine. Apparent ineffectiveness of an antibiotic sensitivity disc or a false negative test for glycosuria might well lead to an incorrect diagnosis and deprive the patient of appropriate treatment.

Before such a preparation can be marketed there must be certification (in the case of antibiotics) or approval of a New Drug Application (in the case of other drugs). For that reason, it is necessary to submit adequate proof of the effectiveness of these preparations before they can be marketed.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
FOOD & DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, Md. 20852 DHEW Publication No. (FDA) 74-3015

Senator HAWKINS. Mrs. Palmadessa, have you or your husband heard anything further from the FDA since receiving that?

Mrs. PALMADESSA. No, no.

Senator HAWKINS. Do you feel that you should have been told more personally?

Mrs. PALMADESSA. Definitely, yes. We should have been told more about the causes of the drug and what it did to my son.

Senator HAWKINS. And the only way I understand that you even heard about the adverse reactions regarding methyl CCNU and kidney failure is from a newspaper article in the Washington Post?

Mrs. PALMADESSA. Right.

Mr. PALMADESSA. Right.

Senator HAWKINS. And you received a rather impersonal printed response?

Mr. PALMADESSA. Right.

Senator HAWKINS. Now, we will direct some time to the Agostinos.

Mrs. Agostino, I understand that your son underwent surgery for a brain tumor in 1974 and then had chemotherapy periodically with methyl CCNU in 1976, which was 2 years later.

Mrs. AGOSTINO. That is correct.

Senator HAWKINS. In 1978, 2 years later—this seems to be in 2-year increments—it was discovered that he had lost 50-percent function in both kidneys. Is that right?

Mrs. AGOSTINO. That is correct.

Senator HAWKINS. Mr. Agostino, prior to the treatment of your son with methyl CCNU, you and your wife signed a form for informed consent. Is that correct?

Mr. AGOSTINO. Yes.

Senator HAWKINS. Did the consent form mention anything about the potential for this drug to cause damage to your son's kidneys?

Mr. AGOSTINO. They told us that he would more than likely develop aplastic anemia and nausea.

Senator HAWKINS. Aplastic anemia and nausea?

Mr. AGOSTINO. Yes.

Senator HAWKINS. And that would be this consent form that I have here, wherein the doctor states that he has fully explained to the patient's mother the purpose of the treatment and the procedures described above and such side effects that are involved in its performance, and signed by the physician?

Mr. AGOSTINO. Yes.

Senator HAWKINS. Mr. Agostino, under what circumstances did you learn that this drug had potential for damaging kidneys?

Mr. AGOSTINO. We brought Kevin, I believe, in 1978 to Children's Hospital for a routine checkup. We got in there and everything was fine. They told us there was no sign of the tumor and no growth; his blood counts and everything were good.

As an afterthought, it was thrown in, "Oh, by the way, he more than likely will develop kidney failure within the next 2 years."

Senator HAWKINS. Mrs. Agostino, I have here an FDA record of the telephone call in which you complained about what had happened to your son. According to this record, your call was made in August of 1978—August 21, in fact. We also have a copy of your letter to the FDA, in which you again stated that you had not been informed of all of the side effects prior to your son's treatment with methyl CCNU.

[The documents referred to follow:]

CONSENT FORM

THE JIMMY FUND AND DANA CENTER CLINIC

nt's Name: KEVIN AGOSTINO Date: 8/22/74

iption of treatment or procedure to be undertaken:
MeCCNU - 150 mg/m² q3wk - p.o.
VINCRISTINE 1.5 mg/m² - q3wk I.V.

I have fully explained to the patient's MOTHER
ure and purpose of the treatment or procedure described above and such
r side effects as are involved in its performance.

Physician's signature

I have been fully informed of the treatment or procedures to be followed
FORBURG including those which are investigational and
en told of the attendant risks and discomforts, if any.

I also have been told of the benefits which may be expected and of alter-
methods that are available. All my questions were answered.

I know that I am free to withdraw my consent and to discontinue partici-
n this treatment at any time.

Patient's signature

or

Mary Agostino
Parent's or Guardian's signature

COMPLAINT/INJURY REPORT

(Shaded items must be completed)

1. COMPLAINT NUMBER: X 014- 060

2. DATE OF COMPLAINT (Month): August 21, 1978

3. FORM OF COMPLAINT: (1) ☒ TELEPHONE (2) ☐ LETTER (3) ☐ VISIT

4. SOURCE OF COMPLAINT: (1) ☒ CONSUMER (2) ☐ OTHER GOVERNMENT AGENCY (3) ☐ TRADE SOURCE

5. COMPLAINANT IDENTIFICATION

a. NAME AND ADDRESS (Include ZIP code)
Mary Agnostino
117 Task Street
Medford, Ma. 02155

b. AREA CODE AND TELEPHONE NO.: 1-617-391-4583

6. COMPLAINT OR INJURY

DESCRIPTION OF COMPLAINT/INJURY: 6 year old son Kevin treated for brain tumors with Methyl CCNU.Helped tumors but gave him kidney failure with approx.2 years to live.Feels drug should not be marketed and something should be done.

7. PRODUCT AND LABELING

a. PRODUCT NAME: Methyl CCNU capsules various doses up to 80mg daily

b. NAME AND LOCATION OF STORE WHERE PURCHASED:
Sidney Farber Cancer Center
Boston, Massachusetts

c. DATE PURCHASED: given over 18month period.

d. PACKAGE CODE: N/A

e. PRODUCT USED (If "Yes," enter date): (1) ☐ NO (2) ☒ YES

f. AMOUNT REMAINING: N/A

8. MANUFACTURER/DISTRIBUTOR OF PRODUCT

a. NAME AND ADDRESS (Include ZIP code): N/A

b. CENTRAL FILE NUMBER:

9. PRODUCT IDENTIFICATION

a. PROBLEM KEYWORD: ADVERSE REACTION ~~Economic deception~~

b. IMPORT PRODUCT: (1) ☒ NO (2) ☐ YES

c. CODES: (1) PRODUCT: 62ICE99 (2) PROJECT: 56R801

10. INJURY OR ILLNESS RESULTED: (1) ☐ NO (2) ☒ YES (If "Yes," complete items a through c)

a. TYPE INJURY/ILLNESS:
(1) ☐ NAUSEA
(2) ☐ VOMITING
(3) ☐ DIARRHEA
(4) ☐ FEVER
(5) ☐ PROSTRATION
(6) ☐ PARALYSIS
(7) ☒ OTHER kidney failure

b. ATTENDING PHYSICIAN: (1) ☐ NO (2) ☒ YES (If "Yes," give name, address, and phone number)
Unwilling to give MD'S name or names.

c. HOSPITALIZATION REQUIRED: (1) ☐ NO (2) ☒ YES (If "Yes," give name, address, and phone number)
As in #7

11. EVALUATION AND DISPOSITION

a. TYPE OF COMPLAINT:
(1) ☐ CONSUMER HAZARD (Illness or Injury)
(2) ☐ POTENTIAL HAZARD
(3) ☐ FRAUD OR DECEPTION
(4) ☒ ADMINISTRATIVE FINDING (New drug without NDA, ETC.)
(5) ☐ ADULTERATED OR MISBRANDED (No hazard involved)
(6) ☐ OTHER (Specify)

b. EVALUATION:
(1) ☐ NOT AN FDA OBLIGATION
(2) ☐ OBLIGATION, NO VIOLATION
(3) ☒ FDA ACTION INDICATED
(4) ☐ VOLUNTARY ACTION INDICATED
(5) ☐ INSUFFICIENT INFORMATION, UNABLE TO EVALUATE

c. DISPOSITION:
(1) ☐ CLOSED WITHOUT FURTHER INVESTIGATION
(2) ☐ REFERRED TO OTHER FEDERAL AGENCY (Close File)
(3) ☐ IMMEDIATE FOLLOW-UP (FD Form 2516a is attached)
(4) ☒ ROUTINE FOLLOW-UP
(5) ☐ REFER TO STATE/LOCAL AGENCY

d. CONSUMER RESPONSE MADE: (1) ☐ NO (2) ☐ YES (If "Yes," enter date)

12. PROCESSING OFFICES

a. OFFICE IDENTIFYING CODES

RECEIVING	EVALUATION	ACTION	DISPOSITION
BOS	HFD-63	BOS	BOS

b. HOME DISTRICT: BOS

c. INFORMATION COPIES TO:

REMARKS

Mrs. Agnostino was very distraught on the phone. Very insistent on knowing what we are going to do about this problem.

8/24/78-Mrs. Agnostino did sign a release form to use this investigational drug but stated at no time did anyone mention kidney damage.Dr.Fosberg's name was mentioned in th
[illegible] Drug was received from Nt'l Cancer Cntr or Nt' Inst. of Health.

NAME AND TITLE: Max Lager/Investigator

DATE: August 21, 1978

FORM FD 2516 (2/78) TEST

MARY AGOSTINO
117 TAFT STREET
MEDFORD
MASS 02155
391-4583

Mr Evans..

I have enclosed copy of consent form for my son Kevin to receive chemotherapy in 1974.

There are two drugs mentioned but the Vincristin was stopped after 2 or 3 times. The Methyl CCNU is the drug responsible for the kidney damage

I was told of two side effects

1/ Nausea during treatment
2/ aplastic aneamia (which he has)

I would appreciate you informing me of this investigation from time to time

Thank you

Mary agostino

Senator HAWKINS. Was there any response from the FDA on this?

Mrs. AGOSTINO. Yes. A gentleman from FDA came to the house and talked to us and we signed consent forms for release of records at the Jimmy Fund, and then we did not hear any more at all. We still have not heard any more.

Senator HAWKINS. When did he come to your home?

Mrs. AGOSTINO. Directly after I wrote that letter; within a month.

Senator HAWKINS. Within a month after this letter?

Mrs. AGOSTINO. Right.

Senator HAWKINS. As a final question before I let Senator Kennedy have his time, could you give us your overall feeling about your experience? We will start with Mrs. Agostino, as a nurse.

Mrs. AGOSTINO. When Kevin went to the Jimmy Fund, he had blood counts done to check for the aplastic anemia. I feel that if the doctors had known about the kidney damage in lab animals, they would have been monitoring the blood chemistries to pick up for early detections of kidney failure, and I think a lot of sadness would have been prevented by that early detection.

Senator HAWKINS. Mr. Agostino?

Mr. AGOSTINO. There seems to be this notion that if everybody does not tell you everything, you are better off. They turn around and tell you your son will more than likely die within a year from cancer; you might as well throw in the rest of the facts because you cannot do much more damage than that.

As I said, here we finally thought we got to the end of the tunnel and somebody comes along and rolls a big rock in front of it again. We had good fortune; God gave us three or four excellent doctors. At one point we were seeing 17 doctors to bring Kevin to where he is.

Kevin is a survivor, and I have often said that 50 percent of all doctors finish in the bottom half of their class; thank God, we did not get the bottom 50. I think that is all.

Senator HAWKINS. But you would have preferred to have known all the truth at the same time?

Mr. AGOSTINO. Absolutely, Senator. You know, it is devastating enough to be told that your son has got—well, they did not know. "Take your son home for the weekend; bring him back Monday and we will operate on him. The operation starts at 7 in the morning; we will let you know by 9." They come down at 9 and say, "We will tell you at 11." They operated for 14½ hours on my son. The doctor did a terrific job; he looked like a man who had been beaten with a bat.

Now, you get him through there and, as I say, you turn around and go through the chemotherapy. We have got 256 trips to the hospitals in 5 years at this point that I can keep track of. All of a sudden, somebody says, "Hey, he has got kidney failure. He may be on a kidney machine within 6 months; he may be on it in 2 years."

And then the FDA comes in and we make out a complaint form, and we never hear a word until your committee contacts us in 1981, 3 years later. I am given to understand that NCI knew in 1971 of the possibilities of renal failure in animals. I really think that it should be right up front, you know, "This is where it is at."

We have no objections to chemotherapy. My son is alive; it works. It is a necessity; it is an evil necessity, which is maybe the correct term for it. But at least lay everything out there in front. It is a tough street to go down; I do not wish it on anyone. But do not get down to the end of the street where you start to see the flowers and say, "Wait a minute, make a left turn; you are going back in the swamp." It does not sit well.

Senator HAWKINS. Thank you, Mr. Agostino.

Mr. Palmadessa?

Mr. PALMADESSA. Would you repeat the question?

Senator HAWKINS. Can you give me your overall feelings about the information you were given or were not given and what you would have preferred—if you were writing the directions for this subcommittee to give to the NCI, in this drug experiment program, from a patient's standpoint.

Mr. PALMADESSA. We were fortunate; ours happened much faster and we lost Michael much quicker. I think there is a lot of room for improvement. I do not think we were told as much as they were told; we were really led in the dark. From day one, we were not told anything.

We used to go to the hospital for just neurological checkups; they kept telling us he looked fine. He was walking like he came out of a bar, but he was fine; we were complaining. They told us we complained too much.

Senator HAWKINS. They told you you complained too much?

Mr. PALMADESSA. Right. They sent us to a liver specialist, who looked at us for 1 minute and said, "It is not my problem." He sent us to an endocrinologist, who said it was not his problem; that he had rickets and he was vitamin D deficient.

They sent us to a blood specialist. He had blood problems; he needed transfusions. His bone marrow was destroyed. His heart was failing; his kidneys were only functioning at 20 percent at this time. Still, they were telling me they did not pick anything up. There is a lot of room for improvement.

Senator HAWKINS. After you learned of the evidence by reading the article published in the Washington Post on April 2, you wrote to the FDA. I would like the record to be perfectly clear that you do not feel that because you consented to the treatment of your child with this drug, that the FDA's response to you and your family was adequate.

Mr. PALMADESSA. No. My wife kept telling me to write them a letter and get a real answer; that that was not the answer. I kept telling her that that was the answer they gave us. We heard no more from them.

Senator HAWKINS. I daresay you will after today, but we are thankful that you came today.

Mrs. Palmadessa, is there anything you would like to add?

Mrs. PALMADESSA. Just a few words. I feel that we went through a nightmare, and Michael is not here with us anymore. If they knew something—just a little more—maybe Michael would have been here, because there was no trace of tumor left the day he died from kidney failure.

Senator HAWKINS. Thank you so much for coming.

Senator Kennedy?

Senator KENNEDY. I want to express our appreciation for your willingness to share what I know has been an extremely difficult and painful experience, and I think you really do a service to us here in the Congress. Most importantly, hopefully, you do a service to other families whose children or loved ones are going to be afflicted with cancer. So, I am grateful for your appearance and the other families who will follow you.

Let me just ask you, on the question of the chemotherapy itself, if you had been given all of the information that you have now, do you think you would have still gone ahead with the chemotherapy?

Mr. Palmadessa?

Mr. PALMADESSA. No. It was 4 years of a lot of torture; it was not 4 years that I could say I had him for 4 years; I did not have him. He never got up and wanted to go to a ball game; he never got up and wanted to go anywhere. It just was 4 years of hell. He just never could adjust to the whole episode.

Senator KENNEDY. Mrs. Agostino?

Mrs. AGOSTINO. I would have gone ahead with the chemotherapy, and being a nurse, I would have certainly had the blood counts monitored very frequently.

Senator KENNEDY. Well, there is one thing you can be assured of, and I think I speak for the members of the committee, and that is that we can and must and will devise a system that adequately informs the patient and their family about the use of experimental drugs.

We can and will develop a system in which the side effects of the drug will be recorded and transmitted to the doctors who are treating those patients. I think we can give you those assurances, and I think your testimony here today will be helpful to us in being able to do so.

I want to thank all of you very much.

Senator HAWKINS. Mr. Agostino?

Mr. AGOSTINO. I really think it would help, when parents go into a hospital and they speak with doctors, if the doctors would consider that you are dealing with a whole package. You are not dealing with a bad kidney; you are not dealing with a brain tumor. We are dealing with a 9-year-old little boy at this point, who is 42 inches tall and has learning problems.

There are more side effects to this than simply not telling anybody. The time involved in going back and forth to a hospital—the best example I know of is that this is the second day that she and I have been out together in 7 years without the boy.

If NCI wants to put out experimental drugs, they have to have them; there is no doubt about it. But maybe NCI should be a little more responsible; maybe NCI should start thinking about, "Well, it is a little boy or a little girl or an old man or an old woman that the stuff is going into, and not a cancer."

Senator HAWKINS. Thank you so much. That is why we are here today. We thank you for coming.

Our second group of witnesses today will be Ms. Sara-Ann Determan and her son, Steven; Mrs. Mildrene Thomasson; and Mr. and Mrs. Robert Bost and their daughter, Cristy Smith.

We have Mr. Bost, Cristy, Mrs. Bost, Ms. Determan, Steve, and Mrs. Thomasson, and I just have one question I would like to ask. I will start with Mr. Bost.

Senator **Kennedy**. Could I just ask one first?

Senator **Hawkins**. Surely.

Senator **Kennedy**. Cristy and Stevie, are you missing school today?

STATEMENTS OF SARA-ANN AND STEVEN DETERMAN, FALLS CHURCH, VA.; MILDRENE THOMASSON, SPRINGFIELD, VA.; AND MR. AND MRS. ROBERT BOST AND CRISTY SMITH, DUNDALK, MD.

Mr. **Determan**. Yes.

Ms. **Smith**. Yes.

Senator **Kennedy**. You are? [Laughter.]

We want you to know we are really grateful that you are here. We hope you will relax. Would you rather be in school or here, do you think, today?

Senator **Hawkins**. That is a hard one. [Laughter.]

That is a hard one to answer.

Mr. Bost, do you feel that cancer patients who volunteer or request to participate in what the physicians call phase I experimental clinical studies should be given complete information, as Mr. Agostino has mentioned, regarding the potential adverse effects of the drugs they would receive? Do you want to get the whole picture as a parent?

Mr. **Bost**. Well, we were very fortunate with Cristy.

Senator **Hawkins**. Can you get a little closer to the microphone, please?

Mr. **Bost**. The majority of the treatment that she had was not experimental; it was standard treatment that they had for her type of tumor. But I would say yes; in any type of treatment, they should give you complete information as far as the side effects are concerned and what is going to happen and what is not going to happen.

In our case, we were very fortunate; they told us what she was going to experience before she experienced it, so we could have an opportunity to explain it to her, too, because she felt that whatever they were going to do, she wanted to know; she did not want to leave anything out.

Senator **Hawkins**. I do not blame you, Cristy; you continue to be that way.

Ms. **Smith**. I will.

Senator **Hawkins**. Mrs. Bost, do you feel the same?

Mrs. **Bost**. Yes, I do. I feel very fortunate that we were given the facts before Cristy did have to experience a loss of hair and that sort of thing, or the nausea and the sickness that she had, because she was extremely sick at times and if I had not expected this in any way, she would have been frightened. But we were informed, I must say.

Senator **Hawkins**. Ms. Determan?

Ms. **Determan**. Steve's treatment has included only one experimental drug; all of the other drugs have well-established efficacy. If anything, there were times when I had the sense I was being given more information than I really could handle. I never had the sense that I was not being given all of the relevant information, nor did we have anything that we did not expect that medicine expected. There was a side effect, but no one anticipated it, and I cannot expect physicians to provide information to us that they do not have themselves.

Senator HAWKINS. Steve, did they talk to you about your treatment?

Mr. DETERMAN. I do not know really how to explain it, but they told me what to expect and I knew what they were going to do.

Senator HAWKINS. So, you were not surprised?

Mr. DETERMAN. Like for a bone marrow, they told me when they were going to stick me, or something, and give me the bone marrow. For an LP, they would tell me when they were going to get the fluid out. So, they never did anything by surprise.

Senator HAWKINS. Good. You are a brave young man. We are proud that you are here with us today.

Mrs. Thomasson?

Mrs. THOMASSON. I was diagnosed as having acute myelomonocytic leukemia in December 1974. I went to Johns Hopkins. I was told that the treatment had would perhaps cause nausea and I might lose my hair. They explained everything to me; I felt that I was well informed. The doctors gave me a 50-percent chance of getting a remission.

They also told me that the normal length of remission was 8 to 12 months, and if I went out of remission, then I could be retreated a second, a third, and maybe even a fourth time. I did not like those statistics, so I asked for a new drug. I said, "Do you have something that you would like to try." They said yes, they did.

Well, within a couple of days, they came back and told me that they would like to try cytosine arabinoside and daunorubicin. I agreed to take the new drugs, not knowing what effect they would have on me, but I felt——

Senator HAWKINS. Were these experimental drugs?

Mrs. THOMASSON. Both drugs had been used separately. So far as we knew then, this was the first time that the two drugs had been used in combination.

Senator HAWKINS. Together?

Mrs. THOMASSON. Yes.

They did not know the proper amount to use. I went out of remission after 18 months, and the second time I was treated, I had less than half the dose that I had the first time. I am the first patient from Johns Hopkins to have had a longer second remission than first. They now have two or three others.

I was fully advised of the treatment. I willingly signed the release forms; I signed releases for any information that would be derived from the study which began with me and is printed in "Cancer," volume 45, No. 5, March 1, 1980.

I do not feel that I had any surprises. I did lose my hair, but it came back. I have since been able to see our son graduate from law school and to see our daughter graduate from college. Under all circumstances, I would go through chemotherapy knowing what I knew when I went through it in 1975 and again in 1976.

Senator HAWKINS. Thank you, Mrs. Thomasson.

Mrs. **Thomasson**. I enjoy every day, and I just hope that the articles that were published will not discourage anyone from participating in chemotherapy treatment. [Applause.]

Senator **Hawkins**. I do not think anyone would disagree with you on that. We had this hearing scheduled prior to the series running in the Post, and wanted to make sure that the message that is given to the world out there and at-large is that there is hope and great opportunity for solving this problem.

But, indeed, as the hearing develops today and with the testimony we will build in this record, we feel that there is opportunity for improvement and we feel that there should be more inquisitiveness—speaking for myself—more inquisitiveness on the part of the patient, and more willingness on the part of the doctor to share with the patient that which he knows.

It has been proven—as the hearings today and Friday will show—that there may be a lot of information out there in the different agencies that does not get filtered down to the attending physicians, which we feel is most important. There are a lot of exciting things happening in cancer treatment and we would like all of the physicians to have that information in their hands, also.

Mrs. **Thomasson**. At Johns Hopkins, I had one doctor come in and advise me of what the treatment would consist of and possibly of the complications. This was one afternoon, and the next morning, a second doctor came in and went through all of this with me again. At that point in time, I signed the second release and chemotherapy was started that afternoon.

So, I think perhaps it is very difficult for you to absorb everything the doctor tells you the first time, because you are quite upset by this, and maybe it would be a good idea to have this discussed a second time with all patients.

Senator **Hawkins**. We appreciate your suggestions, and I think you will find that the monitoring of clinical trials is going to be very important as these hearings unfold over the next few days.

Senator Kennedy?

Senator **Kennedy**. Thank you, Madam Chairman.

I want to express our appreciation on the minority for having this particular panel here this morning. I think it is absolutely essential as I mentioned earlier, that the patients and their families are going to get all the information that is available. And I think the doctors have an important responsibility to make sure that that is communicated to the patients themselves.

I think what we are finding out, or will find out in the course of the hearings, is that sometimes the doctors themselves do not have that information and therefore cannot relate that to the patients. Maybe the Cancer Institute has that information and does not get the information out.

Whatever that bottleneck is in terms of bureaucracy or failed attention, it is something that we have to address in the course of these hearings, to find out how we can develop a system which is going to insure that we are going to get the reports of side effects and get that information back out to the doctors so that they can communicate it.

So, it is important, I think, when we are considering this whole area that we find out where the needs are in terms of meeting responsibilities to the patients and where the bottlenecks are in terms of either reporting the side effects or getting the information recorded as to the adverse drug reaction from the use of experimental drugs. And we are trying to meet our responsibilities in those ways.

Let me, if I could, go with Mrs. Bost. Would you tell us in your own words, really, how you first suspected or were made aware that your daughter might have cancer?

Mrs. BOST. Well, Cristy was 8; it was about 3 days before her 9th birthday when she was diagnosed with a neuroblastoma tumor in her stomach. She just was awakened one night with a pain in her side and it just persisted. So, the following morning, I took her to our doctor and he suggested a second opinion the next day.

There was a blood test taken at that time. The next day, we took her to another physician and they put her right into the hospital, and the following day we were told that she had about a 5-percent chance to survive; that it was a very unusual tumor for her age. Cristy will be 14 in February.

They then started chemotherapy and surgery and a bone marrow transplant and radiation treatment. She has been doing fine now for almost 2 years. She has had no drugs, no medication, no nothing, for 2 years?

Mr. BOST. Yes.

Mrs. BOST. For 2 or 2½ years.

Senator KENNEDY. When the doctor told you, Mrs. Bost, that your daughter had cancer; that the surgery was successful in removing only part of the tumor and that chemotherapy was necessary, what thoughts went through your mind?

Mrs. BOST. Well, they advised surgery first, which they advised seven times; she was operated on seven different times, each time just removing part of the tumor and never really successfully removing all of it. So, it just became a thing that, "We have to do something; we just cannot operate every 2 or 3 months and not get the tumor out."

The bone marrow transplant was suggested at that time. It had been done before, so it was not something that I would think was an experiment. They had done bone marrow transplants before, but Cristy was fortunate because her own marrow was healthy. And before three of her surgeries, they successfully removed her own bone marrow and froze it. At the time of the transplant, they gave it back to her and we began to watch healthy cells grow.

Since the transplant, Cristy has been on no therapy, and I do not believe that the transplant was an experiment. Yet, the doctors really could not say, yes, it will work, or no, it will not. They really did not know, but I was willing to take that last chance because she just could not constantly be operated on every 2 months, as it was beginning to be; every 2 or 3 months, they were doing major surgery again.

So, I was willing to take that chance that, yes, this could possibly give her enough chemotherapy at one time, and total body radiation, and try to kill the tumor that way, because it was impossible to surgically remove it.

Senator KENNEDY. Did you consider that your daughter's doctors were using her as a guinea pig just for experimental purposes?

Mrs. BOST. No, definitely not. I was aware of everything. Anything they did to her, down to a simple test, I questioned, "Why are you doing that? What is it going to accomplish? Will it help her, or are you just doing it for your own information?"

Everything was explained to me because I insisted and I asked, because I knew Cristy, being a child, was not able to, and she certainly did not understand it. And I insisted on knowing everything they did and, if possible, I was there when they did it. I do not feel as though anything was done as an experiment.

Senator KENNEDY. Cristy as I understand, you participated in the decisions, too.

Ms. SMITH. Yes.

Senator KENNEDY. Just tip the mike down; just tip it down a little bit for her.

Ms. SMITH. Yes. If the doctors ever wanted to do like a bone marrow on me or a biopsy or any kind of test that I did not understand what was going on, I made sure that they told me and explained to me what all would be exactly done to me, and if there were any side effects that would happen, you know.

And I was really scared and frightened because I never had the tests done before, and any time they wanted to do something on me, I always wanted to know, you know, what all it would be like.

Senator KENNEDY. How old were you at the time?

Ms. SMITH. Nine.

Senator KENNEDY. Nine. Did you feel like a guinea pig or did you——

Ms. SMITH. No; I never felt that way because I knew that they were doing these tests for a purpose. I knew that everything that they had done to me would be very good because it would help me live, so, you know, I really did not feel that way.

Senator KENNEDY. You have been through quite a time of it—all the operations. How many operations did you have?

Ms. SMITH. Seven.

Senator KENNEDY. Seven operations?

Ms. SMITH. Yes.

Senator KENNEDY. And you had a lot of chemotherapy and radiation?

Ms. SMITH. Yes.

Senator KENNEDY. What is it like? What do you remember about it?

Ms. SMITH. I know that I was petrified all the time because I never knew what would happen to me. I did not know if I would live or die or if I did live, how long. And I was just afraid of everything, and all these different doctors came in my hospital room and I never knew what they were for and what they were going to do to me or tell me.

So, I just went day by day and, you know, just kept fighting for my life, and here I am.

Senator KENNEDY. I suppose, Cristy, there are a lot of children who will be touched by different forms of cancer in this country. What advice would you give them?

Ms. SMITH. I would tell them to always fight for their life and never give up, because if you give up, then, you know, you probably just—it is all over with. But if you keep going day by day and, you know, look on the bright side, then it is always good, you know.

Senator KENNEDY. Mrs. Bost, as you look back on it now, how do you feel about chemotherapy and experimental treatment? Do you have any regrets?

Mrs. BOST. No. As I look back, I would highly recommend that anyone that is diagnosed with cancer to go ahead with chemotherapy. There is always a chance, and I do believe in taking a chance and I do believe in some miracles. And I would highly recommend—do not do nothing; do go ahead with whatever a doctor can recommend for you. That is the way we did it.

We knew nothing at all about it and we put our decisions in the doctors hands because we felt that they were the professional people and they did know a lot more about what they wanted to do than we could understand what was happening. And we trusted their judgment, and I am grateful that we took the changes that we did, even though they were very hard sometimes to say, "Yes, go ahead with another surgery," or "Yes, go ahead with this," knowing the condition that Cristy was in.

But I would highly suggest that, yes, go ahead with any little chance that you are given that it might help; take it.

Senator HAWKINS. Could I interrupt just a moment and ask what this illness has cost you financially so far?

Mrs. BOST. Well, if I live to be 100, I may pay the hospital off one day; I do not know.

Senator HAWKINS. It is a tremendous amount, is it not?

Mrs. BOST. Yes, it is.

Senator HAWKINS. Almost a crippling financial burden.

Mrs. BOST. Yes. I would not know what the hospital would give me right now as what we would owe to them, you know, but it is nothing compared to giving us Cristy.

Senator HAWKINS. Would you mind telling us, at what hospital were you treated?

Mrs. BOST. Johns Hopkins.

Senator HAWKINS. Johns Hopkins, the same as Mrs. Thomasson?

Mrs. BOST. Yes.

Senator KENNEDY. Mrs. Bost, you happen to be a citizen in one of two nations in the Western World—where any mother would have to make that kind of statement or comment. After all you have been through with Cristy, and in terms of the anguish and the suffering and the difficult decisions a parent has to make, then to be financially committed for, I am sure, the better part of your life now in repaying those bills is, I think, just intolerable. I just do not know how families do it.

Obviously, they are so relieved when things turn out well, although others may turn out sadly, but they are obligated for years, and I have seen it all over this country. This may be just a little different issue, but it relates to, I am sure, some of the anguish which any family feels.

Mrs. Determan and Steve—I understand, Steve, you are 10 years old. Is that right? You are ten years old?

Mr. DETERMAN. Yes.

Senator KENNEDY. And, Mrs. Determan, Steve was diagnosed last year as having leukemia?

Mrs. **Determan**. Yes.

Senator **Kennedy**. What were the circumstances in which you learned that your son had leukemia?

Mrs. **Determan**. He had enlarged lymph glands in the back of his neck which were found by his father one night—his father plays with the kids—while watching a football game. The Redskins were losing.

We were very fortunate to have a good doctor who followed it very quickly. Blood tests were done; abnormal cells were seen. A bone marrow test was given and the diagnosis was confirmed.

Senator **Kennedy**. What kind of chemotherapy was proposed, and how did this treatment go?

Mrs. **Determan**. He is on a protocol. He is being treated out at NIH, and he is on a protocol for the treatment of acute lymphcytic leukemia that has very few experimental aspects to it. There were two randomized studies in which he participated. One had to do with a broad spectrum antibiotic coverage when his white counts go way down from the chemotherapy, and the other had to do with a choice between high-dose methatrexate and cranial irradiation, and he was randomized into a high-dose methatrexate group.

There was never any question of our understanding what was going on. Everything was completely described to us, and with respect to one of the tests, we had an option whether or not to participate at all. With respect to the randomization into the high-dose methatrexate, that was on a double blind randomized study, and if we wanted him to be treated at the NIH, the understanding was that we would participate in that study.

Senator **Kennedy**. And he is still getting the chemotherapy?

Mrs. **Determan**. Yes. He will be under active chemotherapy for another 2 years.

Senator **Kennedy**. Do you feel that you were fully informed of the side effects?

Mrs. **Determan**. As I mentioned before, he had an awesome side effect from one of the drugs that no one anticipated. Because of his experience, they are now doing a series of tests to insure that that does not happen to other children.

But other than that, all of the side effects that he experienced, we understood, expected, and were led to believe, and the doctors not only went to great lengths to describe them to me and to Steve's father, but also to Steve, and in forms that he could understand.

His comments before about nothing being a surprise to him have been a very important part of his therapy. He goes out to the hospital with confidence that things will be explained to him before he is subjected to any of the procedures.

Senator **Kennedy**. What about that, Steve? Do you know about the things that are going to be done to you or happen to you?

Mr. **Determan**. Yes, yes.

Senator **Kennedy**. Do they explain it to you?

Mr. **Determan**. Yes, but in the car I always say I will not go through with the things, and I always end up doing it. [Laughter.]

Senator **Kennedy**. That is true about a lot of——[Laughter.]

Senator **Hawkins**. Join the club.

Senator KENNEDY. But you feel that they explain pretty well. Of course, it is always difficult to anticipate, you know, how bad that chemotherapy treatment really is. They can tell you about it, but unless you have been through it, it is awful tough to really understand it.

Mr. DETERMAN. Yes.

Senator KENNEDY. But you feel that they at least gave you pretty good information as to what was going to happen to you?

Mr. DETERMAN. Yes.

Senator KENNEDY. Do you play football now?

Mr. DETERMAN. Yes.

Senator KENNEDY. Do you enjoy that?

Mr. DETERMAN. Yes, sometimes.

Senator KENNEDY. Sometimes. You like being well?

Mr. DETERMAN. Yes.

Senator KENNEDY. Yes.

Mrs. Determan, did you happen to read the series of articles on cancer chemotheraphy in the Post?

Mrs. DETERMAN. Yes, I did. I am here, in part, because of my letter to the editor in response to those series.

Senator KENNEDY. What did you think about them?

Mrs. DETERMAN. Well, I was shocked at what seemed to me to be a very sensationalistic kind of approach to it. And the thing that I was particularly disturbed by because of my experience with Stevie is the absence of any focus on the fact that kids like Stevie are alive today because people who went before us participated in the phase I study.

I have a monumental debt for the life of my son to anonymous people who agreed, when all of his chemotherapy was in an experimental stage, to participate in those phase I studies. And I think it would be particularly unfortunate if the net result of the kind of article that we saw would be to discourage people from participating, both for their own lives and for the lives of people who come after.

I also think it would be unfortunate if, as a result of those articles, important decisionmakers affected the programs such that the kind of successes that Stevie and I have benefited from no longer can happen.

Senator KENNEDY. As a parent, what kind of advice would you give to parents of children who may find out today or tomorrow that their child has cancer?

Mrs. DETERMAN. You have got to be honest with them. You have got to reach out to other people who have been there before, ask as many questions as you want the answers to, listen carefully and do a lot of praying.

Senator KENNEDY. Mrs. Thomasson, I think you have told us a little bit in the early exchange about your case. You were discovered to have leukemia; you told us a little bit about it in the earlier exchange.

Did you happen to see the articles in the Washington Post, and do you think that they presented, you know, a balanced picture of chemotherapy as you understand it?

Mrs. THOMASSON. I read the articles very carefully; I did nothing about it. On the Monday following the articles, I read the letters to the editor, and then I was very upset because I was afraid that a lot of people whose only chance might be through chemotherapy would not go that route.

So, I called the National Institutes of Health and said, "Look, they did not say very much about the survivors. I consider myself a survivor, and I want you to know that I am available to answer any questions relating to my case in the event I am needed." So, that is why I am here.

Senator **Kennedy**. How about the advice you would give to men and women across America that will learn that they have cancer? What guidance and what advice would you give to them as they face difficult decisions?

Mrs. **Thomasson**. The first advice I would give to them is do not accept death; make an effort to do something about it. Go to the best hospital that you can afford to go to and, if possible, I think I would recommend that they should go where they have some grants for special therapy.

In my case, I had white cell transfusions, which were very much experimental at that time. After 72 hours of drugs, off for 8 days, and then 72 hours of additional drugs, then my bone marrow—well, both the malignant and the good cells had been killed. So, that point, for me, was a dangerous period for developing pneumonia or something else. Though I might have been cured of the leukemia, I faced the possibility of dying from kidney infection or heart complications, or something of this nature. At that time, I was given white cell transfusions.

I think it is good, if you possibly can, to go to a major cancer center because I do believe that they have more dedicated doctors and better facilities there.

Senator **Kennedy**. Well, I think all of you have been a great help to this committee and, hopefully, to children who have listened to Cristy and Steve. You are sources of, I am sure, inspiration to other children across the country who are facing some difficult times ahead.

I do not think there is any dispute or debate on the public policy question that individuals should be informed; I would certainly hope not. I do not believe that there is, certainly among this panel. The parents and the children should be informed fully and completely with all of the information.

Having said that, I think they also have to recognize, I suppose, in these treatments that there is going to be a lot of anguish and a lot of suffering and a lot of pain, was there not, Cristy?

Ms. **Smith**. Yes.

Senator **Kennedy**. And that is something that you cannot get away from, you cannot escape. There are no easy answers to dealing with this dread disease or combination of diseases, however you want to define it. And probably if you have not been through it, it is difficult to really understand it, no matter how it is explained.

I want to thank all of the panel very much for helping this committee, and also helping a lot of people who will be affected by cancer.

Senator **Hawkins**. Yes, I reiterate that. This panel has been fortunate in having been treated at a cancer center, which you have all made comments about. That has been one of my concerns.

We have so many thousands of patients being treated at their local hospitals in their small towns and are unable to go to a comprehensive cancer center. We need to make sure that the information that is obtainable and is available at comprehensive cancer centers and at the NCI and all of the other different agencies that have been charged with the mission of curing cancer—disseminate that information to the very bottom of the rung on the ladder of treatment, which is usually the local physician in the small town where the patient is treated.

Early detection has been a theme that we have heard on this panel, and that continues to be No. 1 on the war on cancer's list of priorities. And we are also here today to talk with the other agencies involved in the war on cancer, about the dissemination of information that they have—good and bad information that they have on drugs and the monitoring of experimental drugs that go into phase I and phase II study.

I think it is very important that we all know that this is a very, very expensive illness that touches the lives of all of us. I recall so very well when it touched my family, and it is just not financial; there is a residual effect after the initial trauma the family goes through. It has a lasting impact on children and grandchildren and others.

One of the reasons we are here today is to show that there is great hope and opportunity, and indeed, if some of these agencies had cooperated as well as you have as witnesses, we would be well along the way to treating many, many more patients successfully.

We certainly do thank all of you for coming here today, and excuse you at this time.

The third panel today: Dr. Michael Hensley, Division of Scientific Investigations for FDA; Mr. Laurie Meade, Field Inspector; Dr. R. S. K. Young, Division of Oncology and Radiopharmaceutical Drug Products; Ms. Leah Ripper, Consumer Safety Officer; Dr. Rebecca Wood, Supervisory Chemist; and Dr. David Richman, Supervisor of Pharmacology.

Would the witnesses please take their places at the table—Mr. Meade, Dr. Young, Ms. Ripper, Dr. Hensley, Dr. Wood, Dr. Richman. Before you are seated, please, I would like you all to stand at your chairs and raise your right hands to be sworn in.

Do you solemnly swear that the testimony you are about to give is the truth and nothing but the truth, so help you God?

Mr. **Meade**. I do.

Dr. **Young**. Yes.

Ms. **Ripper**. Yes.

Dr. **Hensley**. Yes.

Dr. **Wood**. Yes.

Dr. **Richman**. Yes.

Senator **Hawkins**. Be seated. Let the record show that all the witnesses responded in the affirmative.

Our second panel of witnesses today consists of six employees from the FDA's Bureau of Drugs. The Bureau is charged with regulating and overseeing the National Cancer Institute's drug development program.

Dr. Michael Hensley is a physician-investigator from the Bureau's Division of Scientific Investigations. From the Division of

Oncology and Radiopharmaceutical Drug Products, the Division that is responsible for processing and reviewing the voluminous investigational new drug submissions from the NCI and industry, we have Dr. Robert S. K. Young—one of the Division's four medical review officers; Dr. David Richman, Supervisory Pharmacologist; Dr. Rebecca Wood, Supervisory Chemist; Ms. Leah Ripper, Consumer Safety Officer; and Mr. Laurie Meade, Field Inspector for the FDA.

On behalf of the subcommittee, I want to welcome each of you here today. Judging from what I have heard and read since I have been involved in this effort, which began last November, prior to my being sworn in as a Senator, I must say that you certainly have your hands full in trying to cope with the endless flow day after day of filings from the NCI and the many drug companies involved.

I want to make sure that everyone here knows that you are the ones on the front line here today, and you are also the ones on the front line at your agency. You are the troops in the trenches, and without you, there would be no program.

I believe that a few of you may have prepared statements for today's hearing. We would be happy to include these in the record, but in the interest of saving time, we will ask that you only respond to our questions.

I would like to begin with Dr. Hensley, who has been with the Division of Scientific Investigations since 1977. And even though you look so young, Dr. Hensley, prior to that you were an associate director for clinical pharmacology at a major drug company.

STATEMENT OF MICHAEL HENSLEY, DIVISION OF SCIENTIFIC INVESTIGATIONS, FOOD AND DRUG ADMINISTRATION; LAURIE MEADE, FIELD INSPECTOR, FOOD AND DRUG ADMINISTRATION; ROBERT S. K. YOUNG, DIVISION OF ONCOLOGY AND RADIOPHARMACEUTICAL DRUG PRODUCTS, FOOD AND DRUG ADMINISTRATION; LEE RIPPER, CONSUMER SAFETY OFFICER, FOOD AND DRUG ADMINISTRATION; REBECCA WOOD, SUPERVISORY CHEMIST, FOOD AND DRUG ADMINISTRATION; AND DAVID RICHMAN, SUPERVISORY PHARMACOLOGIST, FOOD AND DRUG ADMINISTRATION, A PANEL

Dr. **Hensley**. That is correct.

Senator **Hawkins**. Welcome.

Dr. **Hensley**. Thank you.

Senator **Hawkins**. You performed a number of inspections for FDA on matters concerning clinical trials sponsored by drug companies. Would you describe briefly the purpose of these inspections and why are they necessary?

Dr. **Hensley**. Basically, I develop administrative and criminal cases against physicians and pharmaceutical companies who submit false or misleading scientific data to the Government.

The necessity really became a matter of public record as a result of Senator Kennedy's hearings in the midseventies. As a result of his efforts, the Division of Scientific Investigations was created at FDA. I joined it in 1977 as probably the third member of the Division; I have been with it since.

Senator **Hawkins**. As I understand it, the NCI is a drug sponsor, also.

Dr. **Hensley**. That is correct.

Senator **Hawkins**. And are they supposed to abide by the same regulations as drug companies?

Dr. **Hensley**. Absolutely; there is a Federal Register statement to that effect.

Senator **Hawkins**. Have you had occasion to conduct inspections at the NCI in 1979-80?

Dr. **Hensley**. I have.

Senator **Hawkins**. And I believe you were accompanied by FDA Inspector Meade?

Dr. **Hensley**. That is correct.

Senator **Hawkins**. Would you tell us what prompted the inspection in 1979 and what it involved?

Dr. **Hensley**. The 1979 inspection is a somewhat lengthy but interesting story, I think. Mrs. Agostino, as she has noted, wrote a letter in I think late August, early September of 1978 relating her son's problem and the fact that the nephro-toxicity—or kidney toxicity, that is—associated with methyl CCNU had not been on the consent form.

That was referred to me in September, and I subsequently went to the reviewing division in the Bureau of Drugs, talked to the consumer safety officer responsible for methyl CCNU, and also the medical officer, and we looked at the new drug application, which was still on file at the agency at that time, for methyl CCNU.

Neither person I talked to was aware that methyl CCNU might be toxic to the kidneys and, in fact, the new drug application submitted by NCI and Bristol Laboratories stated in several places that no kidney toxicity had been seen in man with the drug.

My concern at that point was should the doctor obtaining the consent from Mrs. Agostino have told her about the kidney toxicity? Obviously, if he did not know, then he should not have told them; there is no way that could have worked out.

So, I set it aside for the time being. I did not discard it because in looking through the NDA, or new drug application, I was struck by the rather sparse nature of the data that had been submitted. That was the first time I had ever looked at an NCI NDA. I came back to it a couple of months later when I had some spare time and decided that I would dredge out the animal studies from the IND or from an area where they were in storage.

In doing so, we found that in virtually every animal species in which the drug was tested, the drug was toxic to the kidneys. It was toxic in a dose-related fashion; in other words, the more you give, the more toxicity you get. In fact, I have in front of me an FDA pharmacologist's review from March 12, 1971, and reading, if I may, from a description of a monkey study, it states:

> The most characteristic finding with this drug was a renal lesion involving the proximal convoluted tubials which did not appear to be related to the root of administration. The intensity of the lesion appeared to be related to and increased with the dose of methyl CCNU and the survival time after treatment. A biochemical indication, such as increased BUN levels, appeared long before the histopathological lesion.[1]

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[1] In the interest of economy, the material referred to was retained in the files of the committee.

So, in other words, in the records of the old studies that had been done back in the early seventies, it was clear from the animal data that kidney toxicity might well occur in humans.

The next question was, "Well, why is Mrs. Agostino's son the first?" And given my background in pharmacology, I really could not believe that there were not more people, particularly more children, who were affected. So, I discussed it with Dr. Lisook, who is my supervisor, and we decided that we would best try to inspect the National Cancer Institute. Dr. Lisook, with his 15 years' experience, felt that it was unlikely that we would be able to inspect them on a so-called for-cause basis, because it was well accepted that the agency had a special relationship with NCI.

Consequently, we decided we would set up a routine inspection and convert it from something of a routine into a for-cause. In other words, we sent out a routine assignment to the district involved. I contacted the district and said, "This is not routine, and I planned to go along."

We had intended to do that in March. Unfortunately, a Senate hearing which was to deal with about 25 of our criminal cases, or more interesting cases, was scheduled and so it was postponed while we prepared for that. The hearing never happened, but in the interim the National Cancer Institute made a submission to the new drug application which essentially confirmed our suspicion, and reported 17 children treated in Boston with methyl CCNU for brain tumor, some of whom had had kidney failure and some of whom had had obvious kidney damage.

[Information supplied for the record follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL CANCER INSTITUTE

MAR 2 1979

IND 7681
NSC 95441
Methyl CCNU

Food and Drug Administration
Bureau of Drugs, HFD-150
ATTN: Document Control Room 17B34
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Enclosed are three copies of a report on a possible adverse drug reaction in patients being treated with Methyl CCNU.

Clinical investigators have been informed, and this material is to be included as an amendment to the IND submission for Methyl CCNU (IND 7681, NSC 95441.

Sincerely yours,

National Cancer Institute
(Sponsor)

Per: ______________________
John S. Penta, Ph.D.
Head, Drug Regulatory Affairs Section
Investigational Drug Branch

Enclosures

cc: Dr. Muggia
Dr. Bono

ADVERSE REACTION REPORT FORM

Date of Reaction:	1973-1978 (just reported)
Name of Drug:	Methyl CCNU
NSC Number:	95441
Investigator:	a) William Harmon, M.D. b) Richard Fisher, M.D.
Institution:	a) Childrens Hospital, Boston b) NCI-Medicine Branch
Protocol Number:	a) Independent protocol b) NCI-MOB in house protocol

Reaction: Dr. William Harmon et. al. report the occurrence of renal abnormalities in patients treated with prolonged courses of Methyl CCNU. Seventeen children with various brain tumors were treated with Methyl CCNU 120 mg/m2 po q 3 weeks for a projected 2 year course. Because of myelosuppression the dose interval was often lengthened and most patients received the drug at an average of 5-6 week intervals. (See Table I for a summary of patient characteristics and treatment course). All 6 patients who received 1500 mg/m2 over at least 17 months developed severe renal damage. The kidneys of the affected 6 patients decreased in size during the course of treatment, but their urinalyses and renal function tests remained normal. After treatment was stopped, their kidneys continued to decrease in size and their renal function tests deteriorated. Four of these patients have developed chronic renal failure, 2 requiring hemodialysis. In addition to these 6 patients, 2 additional patients who received less Methyl CCNU over a shorter period of time, had a decrease in renal size but didn't develop azotemia before they died. Examination of renal tissue from 4 patients revealed glomerulosclerosis in addition to interstitial fibrosis and focal tubular atrophy.

Dr. Fisher at the NCI Medicine Branch reports on the development of renal failure in a 60 year old woman who received 3060 mg of Methyl CCNU. Beginning in March 1976, she received 11 courses at 200 mg/m2 po q 6 weeks over 16 months as adjuvant therapy for melanoma. The patient initially developed severe anemia after 6 courses of therapy. When therapy was discontinued in June 1977 because of anemia (and modest thrombocytopenia), the serum creatinine had risen from 1.1 to 2.1. Despite discontinuation of therapy, progressive azotemia developed and the patient was admitted in December 1977 for evaluation. Serum BUN and creatinine were 79 and 7.3 respectively. No other predisposing factors were present. Urinalysis revealed only 1-5 WBC and trace protein. Urine culture was negative. IVP revealed only bilaterally small (11cm) kidneys. This patient's renal function continued to deteriorate and she is now undergoing hemodialysis.

The IDB has received several reports from the Brain Tumor Study Group of patients who developed renal insufficiency after prolonged courses of

Date:

Signature:

ADVERSE DRUG REACTION REPORT

Methyl CCNU and BCNU. In addition, Schacht et. al. have reviewed 160 patients who received Methyl CCNU or BCNU at New York University during the past 10 years. Fourteen of 17 patients who received at least 6 courses, and all 9 who were given more than 10 courses, developed impaired renal function. Four patients have progressed to uremia.

These cases were presented to the Adverse Drug Reactions Committee on February 13, 1979. It was concluded that these renal abnormalities appear to be definitely related to the use of Methyl CCNU. Although the true incidence of this reaction is unknown, it appears to be related to the administration of higher doses of drug over a prolonged period of time. The IDB plans to initiate review of several earlier protocols to further clarify the incidence of this reaction. In addition, we will notify investigators of this potential adverse reaction and request that they inform us of any similar reactions that they have encountered during treatment.

Michael Jensen-Akula

February 21, 1979 Michael Jensen-Akula, M.D.

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MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTE OF HEALTH

TO : Investigators using Methyl CCNU (NSC 95441) DATE: February 23, 1979

Through : Chief, Investigational Drug Branch, NCI

FROM : Special Assistant to the Chief, IDB

SUBJECT: Report on Renal Abnormalities associated with Prolonged Methyl CCNU Therapy

The Investigational Drug Branch has been recently informed by several independent investigators of the association of severe renal abnormalities with prolonged Methyl CCNU administration. This memo is designed to inform all investigators using this drug of the possible risks involved.

Dr. Richard Fisher at the NCI Medicine Branch reports on the development of renal failure in a 60 year old woman who received 3060 mg of Methyl CCNU. Beginning in March 1976, she received 11 courses of 200 mg/m^2 p o q 6 weeks, over 16 months as therapy for melanoma. The patient initially developed severe anemia after 6 courses of therapy. When therapy was discontinued in June 1977 because of anemia (and modest thrombocytopenia), the serum creatinine had risen from 1.1 to 2.1. Despite discontinuation of therapy, progressive azotemia developed and the patient was admitted in December 1977 for evaluation. Serum BUN and creatinine were 79 and 7.3 respectively. No other predisposing factors were present. Urinalysis revealed only 1-5 WBC and trace protein. Urine culture was negative. IVP revealed only bilaterally small (11cm) kidneys. This patient's renal function continued to deteriorate and she is now undergoing hemodialysis.

Dr. William Harmon et. al. (Childrens Hospital, Boston) recently reported on seventeen children with various brain tumors who were treated with Methyl CCNU 120 mg/m^2 po q 3 weeks for a projected 2 year course. All 6 patients who received 1500 mg/m^2 over at least 17 months developed severe renal damage. Azotemia was generally delayed, insidious and not associated with hypertension or major urinary abnormalities. Four of these patients have developed chronic renal failure, 2 requiring hemodialysis. In addition to these 6 patients, 2 additional patients who received less Methyl CCNU over a shorter period of time, had a decrease in renal size but didn't develop azotemia before they died. A more detailed description of these patients will subsequently be submitted by Dr. Harmon et. al. for publication.

The Investigational Drug Branch has received several reports from the Brain Tumor Study Group of patients who developed renal insufficiency after prolonged courses of Methyl CCNU and BCNU. In addition, Schacht et. al. have reviewed 160 patients who received Methyl CCNU or BCNU at New York University during the past 10 years (Am. Soc. Neph. 1978). Fourteen of 17 patients who received at least 6 courses of drug and all 9 who were given more than 10 courses, developed impaired renal function. Four patients have progressed to uremia.

These cases were presented to the Adverse Drug Reaction Committee on February 13, 1979. It was concluded that these renal abnormalities appear to be definitely related to the use of Methyl CCNU. Although the true incidence of this reaction is unknown, it appears to be related to the administration of higher doses of drug over a prolonged period of time. The Investigational Drug Branch plans to initiate review of several earlier protocols to further clarify the incidence of this reaction. In addition, we request that all investigators inform us of any similar reactions that they have encountered during treatment.

Michael Jensen-Akula

Michael Jensen-Akula, M.D.

MJA:klm

TABLE I

Course of Treatment and Clinical Status of Patients Treated with Methyl CCNU

No.	Age at Dx. (yrs.)	Tumor	Methyl CCNU Duration of Rx. (mos.)	Methyl CCNU Dose (mg/M^2)	Renal Pathology	Present Status
1	11	Brain Stem Glioma	23	2241		Renal Transplant
2	4	Astrocytoma	19	2000	Autopsy	† - Chronic Dialysis
3	5	Meduloblastoma	22	1793	Autopsy	†
4	2	Malignant Glioma	17	1789	Biopsy	Alive - C.R.F.
5	9	Meduloblastoma	21	1529		† - Leukemia
6	7	Glioblastoma	24	1518	Biopsy	Alive - C.R.F.
7	3	Astroblastoma	10	1444		†
8	2	Ependymona	9	1052		†
9	13	Astrocytoma	5	1039		†
10	18	Brain Stem Glioma	6	951		Alive - N.R.F.
11	13	Glioblastoma	6	776		†
12	7	Glioblastoma	5	705	Autopsy	†
13	2	Ependymona	3	675		†
14	6	Meduloblastoma	7	665		Alive - N.R.F.
15	17	Oligodendro-Glioma	2	242	Autopsy	†
16	3	Germinoma	2	230	Autopsy	†
17	8	Meduloblastoma	7	222		†

† dead
CRF: Chronic Renal Failure
NRF: Normal Renal Function

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

MAR 2 1979

IND 7681
NSC 95441
Methyl CCNU

Food and Drug Administration
Bureau of Drugs, HFD-150
Attn: DOCUMENT CONTROL ROOM 17B34
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Enclosed are three copies of the annual progress report for Methyl CCNU (IND 7681, NSC 95441).

Sincerely yours,

National Cancer Institute
(Sponsor)

Per:

John S. Penta, Ph.D.
Head, Drug Regulatory Affairs Section
Investigational Drug Branch

Enclosures

cc: Dr. Muggia
Dr. Bono

ANNUAL REPORT
TO THE
FOOD AND DRUG ADMINISTRATION

METHYL CCNU

IND 7681

NSC 95441

FEBRUARY 1979

Drug Sponsor:

Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment
National Cancer Institute

This report is intended to provide interim clinical information concerning Methyl CCNU since the last report in June 1977.[1] Preclinical data has been provided in the clinical brochure previously submitted.[2]

ADVERSE DRUG REACTION

A. Renal Toxicity

Methyl CCNU was shown to produce acute renal toxicity in animal toxicology studies.[2] and other nitrosoureas have been reported to cause elevated blood urea nitrogen levels in clinical practice.[3] Recently the Investigational Drug Branch has received several reports of renal damage associated with the use of Methyl CCNU.

1. Children's Hospital, Boston: These investigators have recently reported on 17 children with brain tumors treated with brain irradiation and Methyl CCNU 125 mg/m^2 p.o. q 3 weeks. Severe renal damage developed in all 6 patients who received more than 1500 mg/m^2 over at least 17 months. The kidneys of the affected 6 patients decreased in size during treatment, but this was not associated with azotemia, hypertension, or abnormalities in urinalysis. However, after treatment was stopped, further decrease in renal size, associated with deterioration of renal function was observed. Two patients developed chronic renal failure, necessitating hemodialysis. Two other patients have chronic renal failure and one patient had azotemia and small kidneys at the time of his death. The pathologic findings included glomerulosclerosis with thickening and wrinkling of the glomerular basement membrane in addition to focal tubular loss and interstitial fibrosis. These investigators have submitted this report for publication and a pre-print of this data is included as Addendum 1.

2. New York University: Dr. D. S. Baldwin of the Department of Medicine at New York University has retrospectively reviewed the charts of 160 patients treated at New York University with either BCNU or Methyl CCNU, 200 mg/m^2 every 8 weeks. Fourteen of 17 patients who received at least six courses and all nine who received more than ten courses of drug developed impaired renal function, as judged by the elevation of BUN and/or serum creatinine, or decrease in filtration rate as determined by inulin clearance. Four patients have progressed to uremia. No hypertension or significant urine abnormalities have been reported. Renal biopsies in five patients demonstrated tubular atrophy, interstitial fibrosis and glomerular sclerosis. No immunoglobulin deposition or proliferation changes were noted. The investigators plan to obtain a more detailed summary of this information and submit it for publication.

3. Brain Tumor Study Group: Dr. Thomas Strike of the Brain Tumor Study Group has forwarded a detailed case report of a child with a grade IV astrocytoma who received 675 mg of BCNU and 2220 mg of Methyl CCNU over a period of three years and subsequently developed hypothyroidism and renal failure necessitating hemodialysis. A renal biopsy was interpreted as showing "interstitial nephritis." Three other patients receiving BCNU plus Methyl CCNU for malignant brain tumors have apparently also developed hypothyroidism and renal insufficiency, although detailed information on these patients is not available. Some of these patients may have been included in the New York University series described above.

Thus, the administration of Methyl CCNU appears to be associated with the development of renal damage. The lack of earlier reports on this phenomenon appears to be related to the small number of courses of therapy for most patients in earlier trials, associated with the insidious and often delayed appearance of renal disease in the small subset of patients receiving larger doses of drug. The Investigational Drug Branch is presently confirming the data presented and will make plans to inform the participating investigators more fully in the near future.

B. Pulmonary Fibrosis

One patient who received 4100 mg of Methyl CCNU over 24 months was recently reported to have developed pulmonary fibrosis.[4] Open lung biopsy revealed non-specific diffuse fibrosis and no alternative etiology could be determined. Although only this single case has been reported, the temporal sequence and large amount of drug used suggest that this is related to the Methyl CCNU therapy. In addition, BCNU, a closely related nitrosourea, has been reported to cause pulmonary fibrosis in at least 20 patients reported to the Investigational Drug Branch. Although not yet confirmed, larger drug dosages over a longer period appear to play a major role in the development of nitrosourea-induced toxicity.

GUIDELINES

Methyl CCNU has been on "guideline" status since 1976 for use in patients with melanoma, and gastric and colorectal adenocarcinoma. Recent distribution under guidelines is listed in the table below.

PERIOD	NUMBER OF INVESTIGATORS	DRUG DISTRIBUTED		
		10 mg bottles (10 caps/bot)	50 mg bottles (25 caps/bot)	100 mg bottles (25 caps/bot)
10/1/77-9/30/78	1599	1615	1876	936
10/1/78-1/16/79	421	344	458	206

CLINICAL TRIALS

Extensive interest has been demonstrated in the use of Methyl CCNU and at present, 45 cooperative group trials are active. The present results of these trials are listed in Table 1.

SUMMARY AND CONCLUSIONS

Interest remains high for Methyl CCNU, as demonstrated by the large number of ongoing clinical trials. Methyl CCNU appears to have significant activity in melanoma and gastric and colorectal adenocarcinoma. Although it appears to show better response rates in colorectal adenocarcinoma,[21] there is little evidence that this drug is superior to the other nitrosoureas which are commercially available. In addition, newer nitrosoureas such as PCNU and DCNU (Chlorozotocin) have recently been introduced into clinical trials.

We recommend that the present clinical trials be allowed to continue, and that further evaluation of the renal and pulmonary adverse reactions be more fully evaluated.

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5. ECOG Adenda, November 1978.

6. Hahn,R.G., Temkin, N.R., Savlov, E.D., Perlia, C., Wampler, G.L., Horton, J., Marsh, J., and Carbone, P.P. Phase II Study of Vinblastine, Methyl CCNU and Medroxyprogesterone in Advanced Renal Cell Cancer. *Cancer Treat. Rep.* 62:1093-1095, 1978.

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Dr. HENSLEY. Also included in that report was a reference to another study done by Dr. Baldwin from New York. NCI, in their report to FDA, noted that they had informed all their clinical investigators. So, what we had, then, in March was a situation where, indeed, kidney toxicity had occurred, but the public health problem, if you will—you know, whether or not the clinical investigators using the drug knew about it—had been taken care of.

So, we were left with the question of "what did NCI know and when did they know it"—the old Watergate question. So, we decided that we would proceed. We did not get to do the inspection until June, and at that time Mr. Meade and myself did inspect the records of NCI relating to adverse effects with methyl CCNU.

We were told that the first time NCI became aware of it was a January 10, 1979 letter from a Dr. Harmon and Dr. Cohen in Boston. It was this material that had been forwarded to FDA in late February of 1979. In the interim, of course, Doctors Harmon and Cohen had published in the New England Journal of Medicine the results of their study, describing kidney toxicity in children treated with methyl CCNU.

We asked several questions designed to try and determine whether or not there were prior reports, and really could not come up with anything. No one seemed to know anything about anything before January of 1979, except for a single case reported a couple of years before from Los Angeles, but to my mind, that was not a clear-cut case.

[Information supplied for the record follows.]

The Children's Hospital Medical Center
300 Longwood Avenue, Boston, Massachusetts 02115. Telephone: (617) 734-6000

January 10, 1979

VISION OF NEPHROLOGY
TENSION 2446

EXHIBIT C-1
MFR NCI / DCT
DATE July 23, 1979
Inspector LSM

Michael Jensen-Akula, M.D.
Special Assistant to the Chief
Investigational Drug Branch
Division of Cancer Treatment
National Cancer Institute
National Institutes of Health
Building 37, Room 6E12
Bethesday, Maryland 20014

Dear Dr. Jensen-Akula:

I have enclosed a preprint of the article concerning renal failure in children treated with methyl CCNU. As I mentioned in our discussion yesterday, this is a preprint of the article which we have submitted to the New England Journal of Medicine. We have not yet heard from them concerning their desire to publish it. The data, therefore, is not "public information", but I thought that you should have this on file.

As I mentioned, Baldwin's group from NYU presented similar data at the Eleventh Annual Meeting of the American Society of Nephrology in New Orleans, Louisiana in November, 1978. I have enclosed a copy of their abstract for your information also. Even though we differ with respect to the interpretation of the biopsy material, the conclusion reached by them is similar to ours. Thus, it seems that the overwhelming majority of patients who have been treated with high doses of the medication develop significant renal damage which is not apparent until years after the treatment has been stopped. I spoke with Dr. Schacht who suggested that a prospective study might be indicated on the basis of their data. Since we have been able to demonstrate progressive damage during the course of therapy through retrospective data, however, I am not sure that a human prospective study is indicated. I would think that a thorough review of as many patients who have survived at least 2 years after a course of high dose nitrosoureas as possible should be considered.

Exhibit # C-2
MFR AKI / DCT
DATE July 23, 1979
Inspector LSM

Thank you very much for your help in this matter. I will let you know about the specific plans for publication when they become available.

Sincerely yours,

William E. Harmon, M.D.
Director, Dialysis Unit
Instructor, Renal Division
Harvard Medical School,
Children's Hospital Medical Center

WEH/sle

Enclosures

617/734-6000 x 2443 or
thru page operator

EXHIBIT # B-1
MFR [illegible]
DATE [illegible]
Inspector [illegible]

[illegible]th anniversary
CHILDREN'S HOSPITAL OF LOS ANGELES
4650 Sunset Boulevard (213) 660-2450 Mailing Address: P. O. Box 54700 Los Angeles, California 90054

NOV 7 REC'D

November 1, 1977

Dr. Andrew T. Turrisi
Special Assistant to Chief,
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment
National Cancer Institute
Bethesda, Maryland 20014

Dear Doctor Turrisi:

Enclosed is a summary of the history, physical examination, therapy and course on By my calculations he received a total of about 2300 mg of methyl CCNU over a 17-month period.

Also enclosed are the reports on the biopsy of the kidney and selected electron micrographs. As is noted in the EM report I was unwilling to call the changes in the kidney secondary to the nitrosourea although I feel that this is most likely.

The electron micrographs should be returned to me.

The second patient I mentioned as possibly having renal disease and who also received nitrosourea turned out to not have the suspected renal disease. Therefore, our experience is with one patient only.

I hope that these data are of some help. I apologise for the delay in sending the data.

Sincerely,

H B Neustein
H. B. Neustein, M.D.
Director, Electron M-croscope
Laboratory

HBN/j
Enclosures
cc: Dr. S. Siegel
Dr. D. Jamin
Dr. D. Olson
Dr. L. Fishman

EXHIBIT # 8-2
MFR [illegible]
DATE 7/22/77
Inspector [illegible]

SUMMARY

PATIENT: CHLA #48 78 28

DATE: September 6, 1977

The patient is a 5 9/12 year-old boy in whom a fronto-parietal malignant glioma was removed in September, 1973 at age 22 months. Following surgery the patient received radiotherapy to his head and a 17 month course of BCNU. At the time of the craniotomy urinalysis was normal, BUN was 7 mg/dl and hemoglobin 11.9 gm/dl.

During the course of chemotherapy the BUN rose to 25 mg/dl and the hemoglobin declined to 10.1 gm/dl after the first year;at the end of chemotherapy the BUN was 19 mg/dl and the hemoglobin 8.4 gm/dl. Serum creatinine determinations and urinalyses were not done.

In May, 1977, 2 years after the BCNU had been stopped, the patient was seen in the Hematology Clinic because of persistent anemia. Laboratory studies then revealed hemoglobin 7.2 gm/dl, hematocrit 20.8%, WBC 5800, reticulocyte count 1.9%, platelet count 245,000, BUN 37 mg/dl, creatinine 1.1 mg/dl, serum Fe 68, TIBC 264, % saturation 25, bone marrow aspirate and biopsy normal and decreased serum erythropoietin level decreased (0.4 ml serum led to 1.2% Fe^{59} incorporation). Urinalysis was normal. The patient was referred to the Nephrology Service because of azotemia and anemia.

When the patient was seen in the Nephrology Clinic on July 14, 1977 his height was 104.6 cm (below 3rd percentile), weight 18.0 kg (25th percentile) and blood pressure 90/60 mm Hg. Physical examination was normal except for short stature, pallor, alopecia and the craniotomy scar. Urinalysis was normal, and other laboratory data included BUN 32 mg/dl, creatinine 1.3 mg/dl, sodium 142 mEq/l, potassium 3.7 mEq/l, chloride 104 mEq/l, CO_2 25 mEq/l, calcium 8.7 mg/dl, phosphorus 3.8 mg/dl, alkaline phosphatase 169 units, total serum protein 7.44 gm/dl, albumin 4.30 gm/dl, cholesterol 242 mg/dl, uric acid 7.0 mg/dl, glucose 84 mg/dl, total bilirubin 0.2 mg/dl, SGOT 30 units and SGPT 17 units. A renal scan revealed bilaterally decreased function, more severe on the right than the left, and nephrosonography showed slightly decreased renal size bilaterally.

The patient was admitted to the hospital on July 24, 1977 for a percutaneou renal biopsy. An excretory urogram revealed slightly small, poorly functioning kidneys with normal collecting systems.. On July 25 a left renal biopsy was performed.

At his last clinic visit on August 9, 1977 the following laboratory data was obtained: BUN 42 mg/dl, creatinine 1.5 mg/dl, hemoglobin 8.9 gm/dl, hematocrit 27.0% and WBC 5800.

David L. Olson

David L. Olson, M.D.

Dr. HENSLEY. We then said, "Well, since you cannot help us, we will go to Boston and we will talk to Dr. Harmon and Dr. Cohen, and we will inspect their records and see if we cannot sort that out." We asked NCI, you know, whether or not Harmon or Cohen had done the study, who was the investigator and, you know, what was the protocol and where were the records. Ordinarily, before we do an inspection of a clinical investigator, we get such information from drug companies.

And despite some, I think, rather strenuous efforts on their part, they were not able to tell us what protocol had been used or who the clinical investigator was or where the drug had come from, for that matter. Dr. Harmon and Dr. Cohen, it turns out, were people who had discovered this toxicity really by accident.

Dr. Harmon was a kidney specialist who happened to see a child on dialysis who had had a brain tumor. His wife, as I understand it, was a nurse and knew of another child. They put two and two together, and Harmon approached Cohen, who is an oncologist, or cancer specialist, and they did a review of all the charts of children they could find with brain tumors who had been treated with methyl CCNU.

So, going into the inspection of Dr. Harmon and Dr. Cohen, we were in a little bit of an awkward position. FDA has access to patient records, but only the records of patients who have participated in experimental drug trials. We did not know whether Harmon or Cohen had actually done a drug trial; it appeared they had not.

We did not know who at Sidney Farber, or Jimmy Fund, if you will, had really done this study, so we did not know, you know, what would happen if access to records was refused. That was why someone went to see Mrs. Agostino to get a medical release, in the event we were refused access to records. It turned out that Dr. Harmon and Dr. Cohen were extremely cooperative.

They told us the story pretty much as I have told it to you, that it was a chance discovery; gave us their data, and we proceeded to review that. They themselves really did not know who had done the study; they only knew it had happened between 1973 and 1975, primarily. In talking to various paramedical-type people, we discovered that it was most likely that the study had been done by a physician who was no longer there, but now at M. D. Anderson.

I telephoned that physician in a conference call while I was at the hospital near Dr. Harmon's office, and that physician related to me that, "Oh, yes, he clearly remembered," and "No, there was not a protocol." It turned out he had had an idea that maybe this drug might be good for use in brain tumors in children, and he suggested to his residents and fellows that maybe they should try it. And he and a pharmacist had put together a one-paragraph plan of study, or I guess you could loosely call it a protocol, which they had circulated to the house staff.

He said the next time he looked around or turned around, there were 25 kids on the study, and admitted, of course, that it had gotten out of hand. There apparently was not institutional review board approval. The consent form was as you have shown it. The doctor involved was totally unaware of the possibility of kidney toxicity, and that was really why he did not look for it.

I have actually gone past your request for information on 1979.

Senator HAWKINS. That is all right. I would just like to go back. All of this investigation resulted from Mrs. Agostino's letter?

Dr. HENSLEY. That is correct.

Senator HAWKINS. Was your division given free reign when you went to investigate this? Was there any pressure to stop it?

Dr. HENSLEY. Up until—well, let me go back in time. The first thing that happened, I think, when Mr. Meade called NCI to make an appointment for the initial inspection was a call from NCI to people in the management at Bureau of Drugs asking why are they doing this. In fact, I have seen internal memos that your staff provided that suggest that the people in NCI were under the impression that they could not be inspected. They certainly were surprised.

[Information supplied for the record follows:]

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

TO : Director, DCT

DATE: July 11, 1979

THRU : Associate Director, CTEP ____

FROM : Chief, Investigational Drug Branch, CTEP

SUBJECT: FDA "Inspection" of a DCT Sponsored Investigational Agent

The attached memorandum from Dr. John Penta details a request by FDA to meet with members of the DCT to discuss several general aspects of our responsibilities in the conduct of clinical trials with MeCCNU.

It is indeed possible for us to comply with thi[illegible] However, it is my opinion that this request is discour[illegible] memorandum of understanding with the Bureau of Drugs FDA and our mas[illegible] file "Operational Plan and Procedures for Clinical Trials". Aft[illegible] having spent considerable time with representatives of FDA discussing these aspects of our clinical trials activities it seems to be unnecesssary to conduct this exercise once again.

I am of the opinion that we should not comply with this request and that this issue be brought to the attention of Dr. Finkel or Dr. Crout.

Vincent H. Bono
Vincent H. Bono, Jr., M.D.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

TO : Chief, IDB, CTE, DCT, NCI

DATE: July 11, 1979

FROM : Head, DRAS, IDB, CTE, DCT, NCI

SUBJECT: FDA Inspection of Methyl CCNU Clinical Studies Sponsored by DCT

1. Mr. Larry Mead, an inspector with the FDA's Investigations Branch telephoned me and requested a meeting to discuss Methyl CCNU clinical studies being sponsored by the DCT. He will bring a physician with him to discuss the following points with us:

   a. procedures for monitoring clinical studies
   b. evaluation of drug toxicity
   c. how we report adverse drug reactions
   d. how we ensure protocol compliance
   e. procedures for institutional review

2. Methyl CCNU is, of course, a Group C drug and all or most of this information is already in our Drug Master File which we have established with FDA. In response to my questions, Mr. Mead told me he is not a part of the Division of Oncologic Drug Products at FDA and is not affiliated with Dr. Gyarfas' group.

3. He requested we meet with him sometime between July 16-25. Please advise.

John S Penta

John S. Penta, Ph.D.

cc: Dr. Abraham
Dr. Muggia
Mr. Vilk

MEMO OF TELECONS

July 16 and July 17, 1979

Between: Dr. Saul Schepartz
Dr. Vincent Bono
National Cancer Institute

Dr. Michael Hensley/HFD-180

and

Marion J. Finkel, M.D.
Associate Director for NDE/BD

Dr. Saul Schepartz of NCI phoned on 7/16 to state that Dr. Vincent Bono of his staff was concerned because Mr. Larry Mead, an FDA investigator who had phoned NCI for an appointment to review NCI's monitoring procedures with respect to methyl CCNU, was not acquainted with the NCI Master File which describes NCI's procedures. I said that I was not aware that an inspection was planned but that I would speak with Dr. Kelsey or a member of her staff and ask that the investigator acquaint himself with the Master File and that I would phone Dr. Bono to assure him that this would be done.

I spoke with Dr. Hensley, HFD-180, on 7/17/79. He explained the circumstances leading up to the inspection and said that he would accompany Mr. Mead. He said that he would read the Master File relative to the monitoring procedures. We agreed that if he felt it necessary he would ask Mr. Mead to read it as well.

I phoned Dr. Bono on 7/17 and informed him that Dr. Hensley, who was accompanying Mr. Mead, would acquaint himself with the File.

M. J. F.
Marion J. Finkel, M.D.

cc:
HFA-224
✓HFD-180/Dr. Hensley
HFD-100
MJFinkel:eks 7/17/79

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : For the Record

DATE: July 18, 1979

FROM : Chief, Investigational Drug Branch, CTEP

SUBJECT: FDA Inspection of Methyl CCNU Clinical Studies Sponsored by DCT

Background: See memoranda of Dr. John Penta dated July 11, 1979 and of myself dated July 11, 1979.

July 14, 1979. I discussed this request by FDA with Dr. DeVita. We concluded that this should be brought to the attention of Dr. Finkel of FDA by Dr. Schepartz acting in Dr. DeVita's absence.

July 16, 1979. Dr. Schepartz informed Dr. Finkel of the proposed investigation and expressed our concern that our Master File was not being taken into consideration. She said she would find out about the situation.

July 16, 1979. I talked with Mr. Mead of FDA (557-0236) who asked of a meeting time to discuss our "Methyl CCNU protocol". He said that this is a routine inspection of Sponsor and Monitors and is part of a program to more intensely monitor clinical trials including inspection of Government facilities. I told him that our Master File was the result of an inspection that has occurred over the past two years and that I thought we didn't need another inspection. He asked for an appointment anyhow. I gave him a date of July 25, 1979 at 1 p.m. in my office.

July 17, 1979. I received a telephone call from Dr. Finkel who said that she had talked with Dr. Michael Hansley (who will be at the inspection). She told Dr. Hansley and Mr. Mead that they are to read our Master File before the meeting and they will do this. She believews that this will provide them with the proper background for the inspection. I told her that I wasn't sure the inspectors understand our agreement but that we would cooperate and keep in close touch with her about potential problems.

July 18, 1979. I received a telephone call from Mr. Mead who asked that we meet with them much sooner than July 25, 1979 since they will probably want to come back for additional visits. I gave him a new appointment for July 23, 1979 at 10:00 a.m.

Vincent H Bono Jr.

Vincent H. Bono, Jr., M.D.

Mr. **Hensley**. We did get an inquiry in our division from management about it. We reassured them that this was just routine and that we would very carefully look at the drug master file and proceed from there.

Everything else that we did between June and the time we inspected Dr. Cohen was done in a very low-profile manner. We really tried to avoid attracting attention, mostly because we were concerned that if people understood the significance of what we were doing that we would likely not be able to do it.

Senator **Hawkins**. Who would have stopped you?

Dr. **Hensley**. Management in the Bureau of Drugs.

Senator **Hawkins**. By NCI?

Dr. **Hensley**. No. The FDA managers would most likely prevent us from doing it; that was our feeling, at any rate.

Senator **Hawkins**. What kind of a reception did you get from NCI?

Dr. **Hensley**. I think, superficially at least, it was fairly friendly; they were a little cool. They did produce their records. They were, I think, a little bit taken aback by what was going on. They were embarrassed, I think, because they could not give us the answers to the questions that we wanted.

I think things changed dramatically a little further down the way. In March of 1980, having done the inspection of Dr. Cohen and Dr. Harmon, we discovered in their files that NCI had not given us everything that they had; that, in fact, Dr. Harmon had contacted NCI in November of 1978 and had told them about the results of his retrospective study, and that they had provided to him acknowledgement of that contact and, over and above that, had sent him a copy of a previous report from May 19, 1978 from a Dr. Lieberman in New York.

The information that Dr.——

[Note: In the interest of economy, the report referred to was retained in the files of the committee where the material may be researched upon request.]

Senator **Hawkins**. Could I interrupt you just a moment?

Dr. **Hensley**. OK.

Senator **Hawkins**. I have 5 minutes to vote, and I will break right now; do not anybody move.

[Whereupon, a brief recess was taken.]

Senator **Hawkins**. We will go back on the record.

I believe we were discussing what kind of a reception you were given by the NCI during your return visit to NCI. Had we gotten that far?

Dr. **Hensley**. Yes. We were still, chronologically, in March of 1980. I was about to explain that both with regard to internal FDA politics and with regard to what we were doing at NCI, things took a change or a turn—a dramatic turn—in March of 1980, the reason being that Dr. Harmon and Dr. Cohen provided to us copies of documents which showed that the National Cancer Institute had known about their study in November of 1978, and that NCI had also known about another study—in fact, another report of four patients treated with BCNU, which is a chemical relative of methyl CCNU, and methyl CCNU who also developed kidney failure, and that was back in May of 1978.

Now, the documents that Dr. Harmon gave us were copies, I guess, of internal NCI documents, and did have a distribution list on the bottom of the page so that we knew who at NCI had received copies of these documents. Because of this, we felt that the people we had talked to at NCI had not been fully cooperative with us.

We determined we would do two more inspections before our return to NCI. The first was a visit to the commercial sponsor, Bristol Laboratories, and the second was a visit to Dr. Lieberman, who had apparently made this May 1978 report of other children with kidney failure. We did both of those inspections fairly quickly.

Bristol Labs gave us pretty much the same story as the National Cancer Institute, and that was that they had not known anything about kidney failure with methyl CCNU until January 10, 1979—no; correct that. They had not known anything about it until February 23, 1979, which was when NCI made their official report to Bristol

Dr. Lieberman, on the other hand, of course, did confirm that he had made his report to NCI and that it had been distributed in the brain tumor study group, of which he is a member, I believe. He also gave us additional documents which suggested that perhaps there was more to the story at NCI than we had been led to believe.

We decided, then, that we definitely ought to go back to NCI and do a little bit more of an in-depth inspection, interview a few more people, and ask for records that we had not received.

The reception on the part of the Agency or, more appropriately, the bureau management at this time was that, on paper, yes, treat NCI like any other sponsor. However, Dr. Kelsey, who is head of our division, was directed that instead of doing that, she was verbally directed that she should provide to parties at NCI copies of everything that we had; in other words, that we should sit down and meet with them and cooperate with them, and all of that.

Now, on the face of it, that may sound OK, but from my perspective as an investigator trying to develop what is essentially a failure to report case—in other words, a criminal case—that was ludicrous. I cannot imagine that we would sit with any commercial sponsor and show them what we have developed with regard to a possible criminal case involving their personnel. So, my position was shared by, I think, most people in our division.

[Information supplied for the record follows:]

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 5/20/80
FROM: G F Blatt		OFFICE
TO: Fo Kelsey		DIVISION

SUBJECT: Inspection of NCI re Methyl CCNU

SUMMARY

p. 1 of 2

Regarding your intention to Call Dr. Shepartz, NCI.

1. I'm not sure we have any "findings" to provide to them that they don't already have — essentially NCI letters and memoranda. They certainly know the reason we're coming, and an orderly discussion on site would appear to be more productive than the confusion that will undoubtedly be created by sending (in advance) a series of individual documents.
2. If NCI insists on some information in advance, I believe that the previous EIR on NCI-MCCNU can properly be provided, and your 5/6/80 memo to M. Finkel (with her ~~I~~ written O.K. only), WITH THE EXPURGATION OF REFERENCES TO BRISTOL (PAGE 3).
3. Mike Hensley has expressed concern that Shepartz and DeVita were parties to the knowledge of renal toxicity and referred me to Exhibit 3 of the Lieberman EIR. Those documents do not reflect distribution to either. In any case, I think we should expedite the inspection and worry about criminal liability later, a matter for IG, not FDA.
4. My research (?) into this indicates that Bristol had a pending NDA for Methyl CCNU, which was withdrawn on the same date they were

SIGNATURE	DOCUMENT NUMBER

FORM FD 2034 (6/76)

MEMO RECORD	**AVOID ERRORS PUT IT IN WRITING**	DATE 5/20/80
FROM: GFB		OFFICE
TO: FOIC		DIVISION

SUBJECT: NCI - MethylCCNU

SUMMARY

p. 2 of 2

informed of the renal toxicity by NCI. We can reasonably assume they were notified in advance of the letter by NCI. Also, Bristol did not make ~~tt~~ a copy of the NCI notification available when they were inspected. A re-inspection of Bristol seems mandatory.

5. In summary, I recommend that nothing be sent to NCI in advance.

Bob Weidman is the person on my staff who is most familiar with this situation.

George B.

SIGNATURE

DOCUMENT NUMBER

FORM FD 2024 (6/76)

Dr. **Hensley**. Things dragged on for a few months while discussions were had between our division and other people within the Agency. Finally, we did get back to NCI. Interestingly enough, we got back primarily as a result of Senator Kennedy's interest. His staff began, as they periodically do, to review our files in June of 1980, and requested copies of documents relating to the Agostino case and also to methyl CCNU.

They indicated they might have a Senate hearing. I passed that along to people in management, and their response was, "Well, if we are going to have a hearing, we had better do it," so we were authorized to go back. Mr. Meade and myself, in June, did go back to NCI. We laid out for them pretty much everything that we had. We showed them the documents we had gotten from Dr. Harmon and from Dr. Lieberman. We showed them that it looked to us as though they had known since May of 1978 about kidney; yet, had not reported to FDA until February or March of 1979. And their response was, "Well, if you say we knew, then we must have known, but, you know, we do not remember it." And we asked again for documents relating to it.

The documents we were given were pretty much what we had seen before, and there was nothing new in their adverse reaction file. As a last step, we decided we would try to interview one more person—an NCI employee who had been in a key position at the time of the Lieberman report. And that employee not only provided us with additional documents relating to the incidents involved, but told us that yes, indeed, the Lieberman report had been received at the National Cancer Institute in May of 1978 and that he himself, on instructions from NCI management, had reported that to Bristol Labs. In fact, he reported it by telephone and by letter on June 15, 1978.

[Information supplied for the record follows:]

AFFIDAVIT	SAMPLE NO

STATE OF Maryland	COUNTY OF Montgomery

Before me, Laurie S.Meade,Jr., an employee of the Department of Health, Education, and Welfare, Food and Drug Administration, designated by the Secretary, under authority of the Act of January 31, 1925, 43 Statutes at Large 803 (5 U. S. C. 521); Reorganization Plan No. IV, Secs. 12-15, effective June 30, 1940; and Reorganization Plan No. 1 of 1953, Secs. 1-9, effective April 11, 1953, to administer or take oaths, affirmations, and affidavits, personally appeared Andrew T.Turrisi in the county and State aforesaid, who, being duly sworn, deposes and says: I am a Doctor of Medicine presently employed as a Clinical Associate,National Cancer Institute(NCI),NIH Clinical Center, Dept.of ~~Radiology~~ Therapeutic Radiology,Room B3-B38,Bethesda,Maryland 20205. I was formerly assigned as Special Assistant to Chief,Investigational Drug Branch(IDB),Division of Cancer Treatment(DCT),NCI,Bethesda,circa 1978. While in this former position part of my duties involved monitoring of adverse drug reaction reports received from various sources,and communicating that information to my superior, Dr. Vincent H.Bono,and others. Therefore,I am familiar with reports of renal toxicity received while in my former position involving the Investigational New Drug,Methyl-CCNU. A.T.T.

On June 6 and 23,1980 I was visited by U.S.Food and Drug Administration(FDA) representatives Laurie S.Meade,Jr. and Dr. Michael J.Hensley to whom I related my recollection of,and identified several documents dealing with renal toxicity associated with Methyl-CCNU:

I first became aware of renal toxicity in humans administered Methyl-CCNU via a letter,dated 11/1/77,addressed to me from Dr.H,B.Neustein of Children's Hospital of Los Angeles. Approximately six months later,in May-June 1978, Dr.Thomas Strike of NCI's Brain Tumor Study Group forwarded to my attention a letter,dated 5/19/78,from a Dr.Abraham Lieberman,New York University Medical Center,reporting several cases of renal toxicity associated with Methyl-CCNU. As a result of the Lieberman Report,I recall discussing the subject with Dr. Bono at that time.I remember Dr. Bono suggested I contact Bristol Laboratories, Syracuse,N.Y. to inform them of the reports of renal toxicity. I recall at the time,mid-June 1978,I attempted a phone call to Bristol Labs but failed to make contact with a responsible individual because of vacation scheduling.

ATT I informed Bristol Labs via letter,dated 6/15/78, to the attention of the Nitrosurea Monitor, and attached a copy of Dr.Lieberman's letter of 5/19/78.

******CONTINUED ON PAGE TWO**************************

AFFIANT'S SIGNATURE AND TITLE
A.T.T.

FIRM'S NAME AND ADDRESS (Include ZIP Code)

Subscribed and sworn to before me at Bethesda, Md. (City and State)

this 23 day of June, 1980

Laurie S. Meade Jr
(Employee's Signature)

Employee of the Department of Health, Education, and Welfare designated under Act of January 31,1925, Reorganization Plan IV effective June 30, 1940; and Reorganization Plan No. 1 of 1953, effective April 11, 1953.

FD FORM 463a (10/72) PREVIOUS EDITIONS ARE OBSOLETE. ☆ G.P.O. 1975-630-634/1293 3-1

AFFIDAVIT

STATE OF Maryland	COUNTY OF Montgomery

SAMPLE NO

Before me, Laurie S.Meade,Jr., an employee of the Department of Health, Education, and Welfare, Food and Drug Administration, designated by the Secretary, under authority of the Act of January 31, 1925, 43 Statutes at Large 803 (5 U. S. C. 521): Reorganization Plan No. IV, Secs. 12-15, effective June 30, 1940; and Reorganization Plan No. 1 of 1953, Secs. 1-9, effective April 11, 1953, to administer or take oaths, affirmations, and affidavits, personally appeared Andrew T.Turrisi in the county and State aforesaid, who, being duly sworn, deposes and says:

********CONTINUED FROM PAGE ONE**

I also sent Bristol Labs a copy of the letter,also dated 6/15/78, I wrote to Dr. Lieberman acknowledging his letter of 5/19/78 reporting on renal toxicity associated with the administration of Methyl-CCNU.

Also during this same period,Spring and Summer of 1978,I am certain I did not discuss renal toxicity with anyone from FDA or Bristol Labs relative to the FDA's withdrawal of the New Drug Application for Methyl-CCNU.

I have read both pages of this two page statement, and it is, to the best of my knowledge, true and accurate.

PAGE TWO OF TWO PAGES

AFFIANT'S SIGNATURE AND TITLE
X Andrew T. Turrisi, III MD.

FIRM'S NAME AND ADDRESS (Include ZIP Code)
R.O.B. Building 10, Rm. B3-B-38
Bethesda, Md 20205.

Subscribed and sworn to before me at Bethesda, Md (City and State)

this 23 day of June, 1980

Laurie S Meade Jr
(Employee's Signature)

Employee of the Department of Health, Education, and Welfare designated under Act of January 31,1925, Reorganization Plan IV effective June 30, 1940; and Reorganization Plan No. 1 of 1953, effective April 11, 1953.

FD FORM 463a (10/72) PREVIOUS EDITIONS ARE OBSOLETE. ☆ G.P.O. 1975-630-634/1293 3-1

ABRAHAM N. LIEBERMAN, M.D., PC
566 FIRST AVENUE
NEW YORK, NEW YORK 10016

ORegon 9-3200 Ext. 2494

WESTCHESTER
11 Rishbell Rd.
Scarsdale, N.Y. 10583

NEUROLOGY
New York University
Medical Center
Faculty Practice Offices

JUN 1 1978
CENTRAL OFFICE
DIS.

May 19, 1978

cc: BTSG member
Dr. P[illegible]
Ed

Thomas A. Strike, Ph.D.
Central Office Brain Tumor Study Group
Department of Health, Education and Welfare
Public Health Service
National Institutes of Health
Bethesda, Maryland 20014

Exhibit: A (1 of 2 pages)
MFR NIH/NCI/DCT
DATE 6/6/80
Inspector [illegible]

Dear Dr. Strike;

With regard to our recent telephone conversation, this is a follow-up letter. I am reporting here the case of PAL, a boy, who in 1973, at age 10, underwent a resection for a malignant Grade IV astrocytoma. He underwent a subtotal resection and decompression on 1/16/73 for a left occipital posterior-parietal vascular tumor, which was read by our neuropathologists as an astrocytoma with marked anaplasia and was subsequently confirmed by the pathologist of the Brain Tumor Study Group. In accordance with the protocol in existance at that time, this patient was entered into the Brain Tumor Study Group and received whole brain radiation therapy between 2/5/73 and 3/26/73 (5,935 rads). He also received BCNU at a dose of 80mg./m^2. He received three injections: the first commencing 2/14/73, the second on 4/18/73, and the third on 6/15/73; all of which were tolerated well except for a decrease in hematocrit of down to 32 noted with the third injection of BCNU. At this point, it became apparent that the patient could not tolerate intravenous medication. He was a young boy, who was in frank terror at the thought of receiving intravenous injections every eight weeks.

This patient was then changed to Methyl CCNU, and received his first course on 8/14/73 at a dose of 220mg./m^2. Between 8/14/73 and 3/1/76 the patient received a total of fifteen courses of Methyl CCNU. The patient received a total of 675mg. of BCNU, and a total of 2,220mg. of Methyl CCNU. Additional courses of Methyl CCNU were not given because of persistent anemia with hematocrits ranging between 21 and 25%. At this point, the patient was noted to be clinically hypothyroid and was thoroughly investigated for this. At this point, any relationship of the hypothyroidism to the pre-existant treatment with BCNU and Methyl CCNU was not known, nor had there been any reports of this in the literature. All additional chemotherapy had been halted because of the anemia.

On 12/9/76, the patient was noted to have a slightly elevated creatinine of 1.2mg.%. At this time, the significance of this was not appreciated. Subsequently, it became evident that the patient developed renal insufficiency, as manifested by an increasing creatinine of 3.5 on 4/8/77 and an elevated BUN. The patient was thoroughly evaluated at this time, and was noted to have, on the basis of a renal biopsy, an interstitial nephritis. The patient underwent therapy including hemodialysis, and subsequently expired because of complications of sepsis, renal insufficiency, seizures and tumor recurrance. Post-mortem

EX # 3 PAGE 1 OF 7
ABRAHAM N. LIEBERMAN,MD,PC at NEW
BELLVUE HOSPITAL,NEW YORK,NY
3-28-80; INVESTIGATOR SIKORSKY

May 11, 1973
To: T. A. Strike, M.D.

EXHIBIT # A (2 of 2)
MFR NIH/NCI/DCT
DATE 6/6/80
Inspector

examination was not performed. At this time, relationship of renal insufficiency to the chemotherapy was not appreciated.

We have subsequently found three additional patients with brain tumors, who were on long-term BCNU followed by Methyl CCNU treatment for malignant brain tumors. All three of these patients subsequently became hypothyroid and then developed renal insufficiency. Two of them are now being considered for hemodialysis. We are now in the process of obtaining more detailed information on these patients.

The purpose of the present letter is to alert the members of the Brain Tumor Study Group and the Food and Drug Administration to what we feel are the real dangers of long-term chronic therapy with BCNU and Methyl CCNU. We recognize that these complications developed in patients who, had they not received the drug, would clearly have not lived the length of time that they did. Prior to the advent of the nitrosoureas, survival in patients with malignant astrocytomas beyond two years was unheard of. As the number of long-term survivors is now, thanks to the drugs, increasing, we alert people to the possibilities of these complications.

Sincerely,

A N Lieberman
Abraham N. Lieberman, M.D.
Associate Professor

ANL:kf

xc: Michael D. Walker, M.D. - Brain Tumor Study Group, Chairman
Allan E. Dumont, M.D. - N.Y.U., Human Experimentation Committee, Chairman
Mr. Harold Neham - N.Y.U., Pharmacy Department, Director
Jerome L. Shupack, M.D. - N.Y.U., Formulary Committee, Chairman
Joseph Ransohoff, M.D. - N.Y.U., Neurosurgery Department, Professor & Chairman
Robert G. Schacht, M.D. - N.Y.U., Pediatrics, Associate Professor

EX # 3 PAGE 2 OF 7
ABRAHAM N. LIEBERMAN, MD, PC at NEW
BELLVUE HOSPITAL, NEW YORK, NY
3-28-80; INVESTIGATOR SIKORSKY

MEMORANDUM

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

DATE: June 7, 1978

TO : BTSG Principal Investigators

EXHIBIT # C
MFR NIH / NCI / DCT
DATE 6/6/80
Inspector LSW

FROM : BTSG Central Office

SUBJECT: Adverse Effect of Long-Term Nitrosourea Administration

Your attention is directed to the detailed case report of a young patient who had received 3 courses of BCNU followed by 15 courses of MeCCNU. Dr. Lieberman, in his letter (attachment), describes the details of this case, as well as similar findings in three non-protocol patients treated in a similar fashion.

If you have had similar cases, please send the BTSG Central Office the details of your experience so that the group can document these apparent long range effects.

Thomas A. Strike
Thomas A. Strike, Ph.D.
Executive Secretary, BTSG

TAS:kn

(Attachment)

Arlene ..
for your info.
:lh

EX # 3 PAGE 3 OF 7
ABRAHAM H. LIEBERMAN, MD, PC at NEW
BELLVUE HOSPITAL, NEW YORK, NY
3-28-80; INVESTIGATOR SIKORSKY

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL CANCER INSTITUTE
Bldg. 37/Rm# 6E-12
(301) 496-1196

June 15, 1978

Dr. Abraham N. Lieberman
566 First Avenue
New York, New York 10016

Subject: Reported Nitrosourea Toxicity: Hypothyroidism and Nephrotoxicity

Dear Dr. Lieberman:

Thank you for your report to Dr. Strike concerning this observed toxicity. I am told that Dr. Strike is presently surveying the Brain Tumor Study Group to ascertain whether others have seen similar toxicity.

Interestingly, animal toxicology has predicted nephrotoxicity in both BCNU and methyl CCNU. Both the clinical brochure and Wasserman in his 1976 Cancer Treatment Report article have identified renal toxicity associated with nitrosoureas. Streptozotocin, another nitrosourea, has nephrotoxicity as its dose limiting toxicity. Clearly,documentation of this renal toxicity with long term use is not surprising; however, I could not speculate as to its incidence nor whether it is reversible with discontinuation of therapy at the time of observed renal functional deterioration.

Regarding hypothyroidism, this is not routinely assessed in phase I trials. However, I would be even further interested if TSH levels were found to be high in these cases. This would infer a primary gland dysfunction and side step the question of radiation damage to the hypothalmic-pituitary axis. If TSH levels and an endocrine work up is available, please foward copies here.

Thank you for your vigilance. When the results of Dr. Strike's survey are available, you will be notified as to other cases similar to those observed by you.

Sincerely,

Andrew T. Turrisi III, M.D.

Andrew T. Turrisi, III, M.D.
Investigational Drug Branch
CTEP, DCT, NCI

cc: Dr. Bono
Dr. Strike ✓
ADR File
Bristol Lab.

ATT:aa

Special Assistant for Program
Development, DCT

June 15, 1978

Chief, Investigational Drug Branch

Special Assistant to Chief, IDB

EXHIBIT # D
MFR NIH / NCI / DCT
DATE 6/6/80
Inspector KSM

Nitrosourea Toxicity

We have received Dr. Lieberman's report on nitrosourea toxicity. Please find a copy of my reply to him attached.

Renal damage has been described. Its exact incidence isn't known.

Regarding hypothyroidism, there is questions as to whether this does represent drug toxicity.

The results of the survey you are making should be of interest.

Andrew T. Turrisi, III, M.D.

cc: Dr. Lieberman ✓
ATT:aa

EX # 3 PAGE 5 OF 7
ABRAHAM N. LIEBERMAN,MD,PC at NEW
BELLVUE HOSPITAL,NEW YORK,NY
3-28-80; INVESTIGATOR SIKORSKY

[redacted]

[redacted]

Enc E
NIH/NCI/DCT
6/23/80
CSm

June 15, 1978

Bldg 37/Rm# 6E-12
(301) 496-1196

Bristol Laboratories
Monitor for Nitrosoureas
P.O. Box 657
Syracuse, New York 13201

Subject: Reported Nephrotoxicity and Hypothyroidism

Dear Sir:

Enclosed please find a case report of a patient treated with both BCNU and methyl CCNU for malignant glioma. This patient also received radiotherapy, and subsequently developed both hypothyroidism and renal failure.

Renal damage has previously been predicted by animal toxicology, and clinically observed.

This report is being evaluated here.

Sincerely,

Andrew T. Turrisi, III, M.D.
Investigational Drug Branch
CTEP, DCT, NCI

Enclosure
ATT:aa

[redacted]

Dr. **Hensley**. If you go back in the history of the new drug application, you will find that, coincidentally, it was on that very same date that Bristol withdrew their new drug application for methyl CCNU from consideration before the agency.

So, the bottom line is that, you know, we found out that NCI had known and they had not given us everything they had. Certainly, the individual we found was able to give us more. We felt at that time that we had developed a case for failure to report, and so we recommended that consideration be given to prosecution of certain individuals involved.

Senator **Hawkins**. Inspector Meade, are you in agreement with Dr. Hensley on this?

Mr. **Meade**. Yes, I am. However, for the record, I am not with the Bureau of Drugs; I am with a field branch of FDA.

Senator **Hawkins**. Field——

Mr. **Meade**. Field branch. To be more specific, I am with region III, Baltimore District, FDA.

Senator **Hawkins**. Field branch of FDA?

Mr. **Meade**. We are not part of the Bureau of Drugs chain of command. I want to make sure everyone understands that. Yes, I do agree with Dr. Hensley as to what we found during our inspectional visits in July of 1979, and again in June of 1980. The visits were to the Division of Cancer Treatment's Investigational Drug Branch.

Senator **Hawkins**. Thank you, Mr. Meade.

If you would; Dr. Hensley, would you briefly sum up your impression of this entire matter now?

Dr. **Hensley**. Very briefly, it appears that NCI knew that the drug methyl CCNU carried with it a predictable and dose-related side effect that was kidney toxicity. It was reasonable to expect that since it had been seen in virtually all the animal species in which it was tested that it might show up in humans. It was not looked for.

The clinical investigators who used the drug, at least in Boston, were not aware of it as a possibility. Because it was not looked for, some time after the fact—in fact, years later—by chance, Dr. Harmon and Dr. Cohen happened to notice that there were some children around with kidney failure and that they had had methyl CCNU.

The bottom line is that when that report from Harmon and Cohen came to NCI, they failed to submit it to FDA in a timely fashion. Regulations on such things state that an adverse effect associated with the use of a drug, whether or not it is known to be attributable to the use of the drug, must be reported. If it is alarming—and I should think this is an alarming adverse effect—it should be reported immediately.

We recommended from HFD-180—or at least I recommended, and my supervisor—that consideration be given to prosecution of individuals who had known but not reported, and that included individuals from NCI and from Bristol Labs. Parenthetically——

Senator **Hawkins**. What happened?

Dr. **Hensley**. Well, parenthetically, I might say that the people who develop criminal cases after we get through with them—the Compliance Branch—did do a followup at Bristol, and Bristol, when shown the documents we had, were suddenly able to discover those documents in their files. And, yes, they had received that report.

Now, what came of it was not a prosecution, but two letters; one that issued to NCI outlining what we had found, and another had issued to Bristol Labs. Replies were received from both parties, and so far as I know, the case is going no further.

Senator HAWKINS. Did you refer your findings to the Inspector General?

Dr. HENSLEY. I did discuss it with the Office of Inspector General. That goes back to March 19, 1980, when Dr. Kelsey, faced with what she felt were conflicting instructions from management and not knowing exactly how to proceed, recommended that this case be referred to the IG, since Department of Health and Human Services employees were involved.

That referral did not occur at that time, but subsequently I did discuss this with the Office of Inspector General as part of another discussion on some related matters, and they did do some sort of followup and investigation.

Senator HAWKINS. When did you make that referral?

Dr. HENSLEY. I think September or October 1980; I do not have a precise date.

Senator HAWKINS. Do you know what has happened to it?

Dr. HENSLEY. No; I do not. I know that they began to investigate, but what happened after that I really do not know.

Senator HAWKINS. A final question, Dr. Hensley, on methyl CCNU: Do you feel that the Agostino family and the Palmadessa family have reason to be disturbed over the consent form that they signed for their children, since it did not contain the information on the potential kidney toxicity?

Dr. HENSLEY. Before I answer that, I have to make clear that the Palmadessa family were included in Dr. Lieberman's—or the Palmadessa child was included in Dr. Lieberman's study, and the Agostinos, of course, were in the Harmon-Cohen study.

Senator HAWKINS. Right.

Dr. HENSLEY. Neither center, so far as we know, was aware of kidney toxicity.

Senator HAWKINS. Neither what?

Dr. HENSLEY. Neither medical center, neither the one in Boston nor the one in New York where the Palmadessas were treated—or the Palmadessa child was treated—were aware of kidney toxicity as not only a possible but a probable adverse effect. If they are not aware, how can they know to put it in the consent?

There is a failure here, but I think it is a failure on the part of NCI, not on the part of the clinical investigators. Because of that, we have not taken any action against the clinical investigators. We felt the appropriate party to take an action against was NCI.

Senator HAWKINS. It would be NCI?

Dr. HENSLEY. Right.

Senator HAWKINS. I would like to move on now to another anticancer drug known as DHAD, and it is used in NCI-sponsored clinical trials, Dr. Hensley. FDA was kind enough to let us borrow—"us" being the subcommittee—you for a few days so that you could review the entire file on this drug.

There have been more than 25 cases of congestive heart failure possibly associated with DHAD over the past several months, including some deaths of patients. And I learned during the subcommittee's investigations that these drugs are first tested in animals—mice and dogs, and sometimes in rats and rabbits. The animal studies are designed to determine whether a given drug may cause various toxicities—damage to the kidneys, liver, heart, and other organs. These findings are used to calculate a safe dose in humans.

And if you agree with that observation—maybe it is oversimplified; I am trying to describe it in layman's terms—would you tell us what you found in the investigational new drug files on the animal data pertaining to DHAD?

Dr. HENSLEY. That is a pretty good summary. The animal data on DHAD—really, there are two parts: What was in the official submissions by the National Cancer Institute to FDA, and the material that was not submitted.

The material that was submitted consists——

Senator HAWKINS. You are saying there are two parts?

Dr. HENSLEY. I am saying there are two bodies of data; one that was submitted and one that was not.

Senator HAWKINS. One was submitted and one was not?

Dr. HENSLEY. That is right.

The one that was submitted—the official IND application——

Senator HAWKINS. "IND" meaning investigational new drug?

Dr. HENSLEY. Right. An IND is really like a contractual arrangement between FDA and a sponsor that permits the sponsor to ship the drug in interstate commerce. And as a part of getting an IND, they submit their animal studies and their chemistry, and that kind of thing.

The IND submission—the original one—on DHAD was made September 28, 1979. It contained animal studies—studies done with two or three different salts of DHAD, which is a relative of a well-known drug called Adriomycin.

The bulk of the information in the IND said that the drug was not toxic to the heart. This was important because Adriomycin, the close chemical relative of this drug, is quite toxic to the heart, and that is a well-known adverse effect. And having done chemotherapy myself for some time, I can tell you it is a very alarming adverse effect.

DHAD was thought to be a relatively safe drug—one that would at least maybe go after the same tumors that Adriomycin does, but with less damage to the heart. At any rate, the other body of data in the IND were two studies that had been done at Ohio State in dogs.

These studies were what are called acute studies. In other words, they were large, single doses given intravenously in this case. These studies showed that all of the dogs treated in all of the different dose groups with DHAD died within 12 hours of the time they were treated. They died a cardiovascular death, which means their heart function began to fail. They developed changes in the electrocardiogram and then died.

This material, in all fairness, was in the IND. So, in the IND, just to sum it up, there was a lot of data that said the drug is safe to the heart, and these were studies done in monkeys and rats and dogs. And then there was another small piece of data—these two studies from Ohio State—that said the drug may not be safe, at least if you give it in large doses intravenously.

Now, as I said, there was other data that was not submitted to the IND. This other data was of two kinds. One is a study done in rabbits, which was on file at the National Cancer Institute at the time the IND submission was made. And this study did show that the drug was toxic to the heart.

There were other studies, I have learned within the last couple of days, that the commercial sponsor, Lederle, also involved with this drug, had paid for in mice and rats which strongly suggested that this drug was toxic to the heart. There were lesions in the heart in these mice and rats, but because of the nature of the studies that were done, they were unable to say for sure.

So, what we had was a certain amount of information that was certainly damaging to the drug that was not submitted to the IND.

Senator **Hawkins**. Why?

Dr. **Hensley**. I really do not know. An inspection was done by a friend of mine, Dr. Turner, at NCI, but I do not think they have developed any reasons as yet. I have seen a memo from a former NCI staff person which suggests that some of the management people at NCI did not feel that the rabbit study was truly predictive.

And in all fairness, the Lederle studies on rats and mice, although we know they existed, I cannot prove that they were in the hands of NCI prior to the new drug application being—I am sorry—prior to the IND being submitted. So, it is probably a combination of a judgment that was made and maybe some trouble in communication between Lederle and NCI. That is just speculation, though.

Senator **Hawkins**. In your review of the 33 protocols contained in the NCI filing, did you find any with warnings of cardiotoxicity associated with DHAD?

Dr. **Hensley**. Yes. I found 2 out of 33. Again, the theme here is much like methyl CCNU. The investigator's brochure that was prepared by Lederle for the National Cancer Institute and distributed to cancer chemotherapy investigators by NCI fails to warn that this drug may be toxic to the heart.

Not surprisingly, therefore, 31 out of the 33 protocols I found in the IND either say the drug is not toxic to the heart or describe it as being fairly safe, or they very much softpeddle the animal studies. There were two protocols from the phase I working group that did acknowledge—in fact, quoted in great detail from the two dog studies I previously mentioned. How those people knew and the others did not, I really do not know.

Senator **Hawkins**. We are going to get into some recommendations to solve that problem shortly. But do you have the letter dated August 24? It is from a physician that lends support to your findings—from a physician at a cancer center. Would you kindly refer to that letter and explain the significance of it?

Dr. **Hensley**. Yes; I do. As you have mentioned, there were a number of patients who developed cardiac toxicity from the drug, or appeared to have. There were six patients, by my count, who have died in heart failure, and presumably this is related to the drug.

This is a report on one of these patients. Page 2 of the letter notes that this was a 14-year-old boy with a bone tumor, who had had Adriomycin, the chemical relative of DHAD, and had developed cardiac toxicity from that. It goes on to say that the child was treated with DHAD and developed intractable—in other words, not treatable—congestive heart failure and died.

Specifically, I will read you one sentence. The doctor says, "At that time, we knew that his cardiac function was compromised"—and this means prior to starting the DHAD—"but it was stable, and we were not aware of the cardiotoxicity of DHAD." It is the same thing; this doctor, like most of the other doctors, apparently, did not know this drug might be cardiotoxic.

[Information supplied for the record follows:]

The Johns Hopkins Oncology Center

Pediatric Oncology
301/955-8816

August 24, 1981

Louise Lev, M.D.
National Cancer Institute
Landow Building, Room 4C37
Bethesda, Maryland 20205

Dear Dr. Lev:

This letter is in reference to Christopher Wilkins, JHH #187 91 61. Christopher was first admitted to the Johns Hopkins Hospital on July 9, 1979, with a history of right leg pain a few weeks after being hit there by a frisbee. It became obvious through diagnostic studies that he had an osteosarcoma of the right tibia and he had an above the knee amputation on July 13. At that time, his metastatic work-up revealed no evidence of disease and he was started on an adjuvant protocol with vincristine and high dose methotrexate. He had some difficulty with hepatotoxicity during this protocol and for this reason, his therapy was switched to adriamycin on September 24, 1979. He received 30 mg/M^2 x 3 days for a total course of 90 mg/M^2 at approximately four week intervals over the next several months to a total life time dose of 540 mg/M^2 which was completed in February, 1980. In April, 1980, he was admitted with evidence of congestive heart failure and at that same time, in fact, on the same diagnostic chest x-ray, he was also noted to have multiple pulmonary metastases. He also had a small bilateral pleural effusion with cardiomegaly and possible small pericardial effusion as well. At that time his ejection fraction was also noted to be 22% on echocardiogram and his left atrium was seen to be enlarged. His cardiac studies up until that time had been normal with the exception in retrospect of non-specific T-wave flattening seen in the inferior leads in January 1, 1980, which persisted through his studies in April. He later developed a prolonged QT-interval consistent with adriamycin cardiotoxicity. His congestive failure responded to fluid restriction and digitalization. Once his cardiac status had stabilized, it was elected to control his pulmonary metastatic disease with surgery and he had thoracotomies for resection of pulmonary nodules on 5/19 on the right side, on 6/5 on the left side, 8/15 again on the left side in 1980. On 11/25 and on 1/8/81, he also received some low dose methotrexate in the time of his surgery. Throughout that time, his cardiac function studies showed persistent poor left ventricular function and flattened septal motion. The ejection fraction remained around 45%. There were diffuse non-specific T-wave changes on his cardiogram. Chris

600 North Wolfe Street, Baltimore, Maryland 21205

had limited himself to a very sedentary life style and in fact, in March and April, 1981, he began complaining of tenderness in his left wrist which eventually proved to be another metastatic lesion. This made it difficult for him to walk on crutches and he was confined to a wheel chiar. For this reason, his cardiac functional status may have been less good than we thought since although he appeared compensated, he engaged in very little physical activity. On April 22, 1981, he was entered on the DHAD study and he received 18 mg/M^2 on April 22, on May 13, and again on June 22. At that time, we knew that his cardiac function was compromised, but it was stable and we were not aware of the cardiotoxicity of DHAD. He did show a fall in white count with a nadir of 440 on 6/11 nine days after the third dose with 20% neutrophils at that time. He did not have any clinical problems with this low white count which recovered slowly. On June 26, 1981, he had a CT scan of the head which showed an enhancing lesion throught to be an intracranial metastasis. The left arm metastasis showed no response to the DHAD. By June 29, his white count had returned to 5600 with 64% polys; his hemoglobin and platelets did not fall. On July 6, 1981, after two days of vomiting and generalized discomfort, he was admitted with severe intractable congestive failure. At that time, the echocardiogram showed virtually no wall motion at all with the mitral valve essentially not closing. He became hypotensive and was declared dead at 15:10 p.m. on that date. Preliminary post-mortem examination is available which showed chronic congestive heart failure, very mild dilatation of the heart with mild softening of the myocardium, a small serous pericardial effusion of 50 cc, scarring and adhesions of the lungs secondary to multiple thoracotomies with some restrictive lung disease, congestion and mild edema of the lungs, atelectasis of the lungs, a 50 cc serous effusion in the right pleural cavity. On microscopic examination of the heart, there was both old and new degeneration of myocardial cells. There was some evidence of persistent intrathoracic tumor. The final pathology report is not yet available, but will be forwarded when it does become available.

In summary, this is a 14 year old boy diagnosed as having osteosarcoma in 1979, who completed a total dose of adriamycin of 540 mg/M^2 in February, 1980 and went into congestive failure in April, 1980. His congestive heart failure had been stable for a year and in fact, he had tolerated multiple thoracotomies for control of metastatic disease. At the time of appearance of a bony metastasis in April, 1981, it was elected to start him on DHAD and in the course of this study, he developed intractable congestive heart failure and died. We feel that this is an important complication of DHAD therapy and wanted to submit this formal report to you. As you know, he was officially entered on the Pediatric Oncology Group protocol 8139 and in view of thie several reports of cardiomyopathy, that protocol has been amended such that patients with prior congestive heart failure will not be eligible for DHAD therapy. Patients who have had more than 540 mg/M^2 prior to anthracyline therapy will not be eligible and the ejection fraction must be within normal limits prior to entry on study. Please telephone me at (301) 955-8816 if you require any further information. As I noted, I will try to forward the final pathology report to you once it becomes available.

Sincerely,

Brigid Leventhal MD

Brigid G. Leventhal, M.D.
Director
Division of Pediatric Oncology

BGL/cbj

cc: T. Vietti, M.D.
R. Lenhard, M.D.

Mr. **HENSLEY**. Consequently, they did not look for it, and I guess it is reasonable to presume that they probably did not put it in their consent forms, though we really do not know that yet.

Senator **HAWKINS**. Do the protocols contain any instructions regarding the monitoring of heart activity?

Dr. **HENSLEY**. Yes. It varied considerably. There were a couple of centers that were very, very aggressive about monitoring cardiac functions. There were many others, however, that, for example, would get electrocardiograms every 6 weeks.

I can tell you from having done a lot of phase I work myself with drugs other than cancer drugs that even if this were, let us say, a psychoactive drug like Valium, you would, in phase I, be getting cardiograms more than every 6 weeks, much less this drug.

Senator **HAWKINS**. So, based upon your analysis in just these two instances, would it be fair to say that lifethreatening matters concerning the use of DHAD and methyl CCNU slipped through the cracks at both NCI and the FDA?

Dr. **HENSLEY**. Yes; I guess that is fair. It slipped through the cracks at FDA because neither investigator's brochure—and those things are reviewed by FDA—made a point of it—made a point of the adverse effect.

It is possible that in the course of reviewing these submissions, in fact, some of our reviewers may also have made some mistakes in permitting the studies to go forward. I do not think we really know enough yet to make that call.

Senator **HAWKINS**. Thank you. We certainly appreciate your assistance in examining these complex and important issues.

Mr. Meade, you have been with the FDA since 1969?

Mr. **MEADE**. That is correct.

Senator **HAWKINS**. And conducted numerous inspections at research institutions; is that correct?

Mr. **MEADE**. Yes, madam, that is correct.

Senator **HAWKINS**. And more recently, you and a scientist from FDA conducted an inspection at the NCI, beginning in July of this year?

Mr. **MEADE**. Yes.

Senator **HAWKINS**. Could you briefly summarize the findings of the inspection by referring to the first page of your report?

Mr. **MEADE**. Do you want me to go into the reason for the inspection?

Senator **HAWKINS**. Yes; the findings.

Mr. **MEADE**. This was a directed inspection of the National Cancer Institute's Division of Cancer Treatment. It was prompted by the Bureau of Drugs' Division of Scientific Investigation's information that there were two animal toxicity reports related to DHAD that were conducted for the NCI, but not submitted to the Food and Drug Administration with the IND application. That is what Dr. Hensley has just discussed.

Second, the Bureau of Drugs had learned there were a number of adverse reactions and fatalities involving liver toxicity related to Indicine-N-Oxide; third, the drug DCF, Deoxycoformycin had been administered to patients at M. D. Anderson Hospital in Texas without approval of the protocol by NCI.

Senator **HAWKINS**. Without the approval of the protocol?

Mr. **Meade**. Yes; and last, that another drug, 5-Methyltetrahydrohomofolate, a radio-labeled drug, which was intended for use in animals had also been administered to humans at M. D. Anderson Hospital without approval of NCI or the Food and Drug Administration.

Those were the reasons behind our visits, which started in July and concluded in September of this year. Basically, what we found by reviewing their records were the two animal toxicity studies dealing with the drug analogs related to DHAD. Officials at NCI admitted they had the reports there, but had not submitted them to FDA.

We also confirmed that NCI failed to report the adverse reactions and deaths related to Indicine-N-Oxide in a prompt manner to FDA. And we did confirm that the drugs DCF and 5-Methyl had been administered to humans as reported.

Senator **Hawkins**. Your report indicates that you and your partner spent a lot of time reviewing the files at NCI. Is that an easy job? How would you characterize the condition of the files, and did you have difficulty finding what you needed and what you thought should be in the files as a professional investigator?

Mr. **Meade**. It was a very difficult job trying to review the files, mainly because I think the filing system in the investigational drug branch at the Division of Cancer Treatment is so disorganized. We would request a file on a particular drug, stating "We want to see your entire file on that drug." NCI officials had to run around to each office and to each doctor or employee in that branch asking "Do you have a file on this particular drug?"

Sooner or later, somebody would bring us an arm full of files. However, we could not find one complete single file or file cabinet, or whatever, at the investigational drug branch which was labeled drug X or drug Y, where we could just look through that file and find everything we wanted to know about that one drug.

Instead, different employees in the branch would have their own file. I do not think there was one official file for any drug on which we requested information.

Senator **Hawkins**. There is not one official file on one drug?

Mr. **Meade**. Not to my knowledge. However, the investigational drug branch does maintain IND files, which I believe they refer to as their official file. Our review of these files revealed nothing more than duplicate copies of materials already submitted to FDA. Of course, this was not what we were looking for.

Senator **Hawkins**. They are all over the ball park?

Mr. **Meade**. Yes, that is correct—part of a file here, part of a file there. But, there was not one file or filing system within the investigational drug branch to serve as a central repository of information on each drug.

Senator **Hawkins**. On page 8 of your report, you state that two supervisory physicians in the NCI's drug development program expressed concern that you and your partner were on a fishing expedition—a comment that I would characterize as being less than friendly, especially from a sister agency, as they call each of you.

Was the level of cooperation less than what you would have desired?

Mr. **Meade**. I think the level of cooperation during this visit was more straightforward than my previous visits in 1979 or 1980.

Senator **Hawkins**. It is bad, but the good news is it is getting better? —

Mr. **Meade**. Yes, more or less.

In addition to the situations described on page 8 of my report, I was informed by my coinspector, Dr. Turner, that following the first day of our visit when he returned to FDA headquarters, someone from NCI had already been on the phone complaining to higher ups in the Bureau of Drugs that we were there on a fishing expedition, tying up their staff needlessly with our requests.

Senator **Hawkins**. Did they volunteer any information? Did NCI volunteer anything? Did you have to ask them for everything?

Mr. **Meade**. Yes, they did volunteer that six rather than four patients, as previously reported, were involved in one of the unauthorized studies at M. D. Anderson Hospital. But, basically, we had to ask directly for everything we got, and repeatedly ask for it.

Senator **Hawkins**. It would appear that your fishing expedition produced some fish, did it not?

Mr. **Meade**. Yes.

Senator **Hawkins**. In your opinion, do you feel that this latest inspection raised questions about the NCI's drug program that should be answered in the interest of improving this program?

Mr. **Meade**. Yes, there is plenty of room for improvement.

[Information supplied for the record follows:]

DATE ASSIGNED: 7 /81 PRIORITY: DATE INSPECTED: July 16-Sept. 4, 1
EMPL NO: 321
CENTRAL FILE NO.: 1119714 JD/TA: 13 PHONE: 301-496-5223 GRP:

NAME: NIH/NCI/Div. of Cancer Treatment STREET: NIH

CITY: Bethesda COUNTY: 031 STATE: MD ZIP: 20205 DISTRICT:

ENDORSEMENT

This was a directed inspection conducted with Dr. Gurston Turner, covering NIH/NCI actions as sponsor for clinical studies on several oncolytic drugs. Previous inspections in 7/79, 9/79, and 6/80 revealed NCI had not promptly reported severe adverse reactions to Methyl-CCNU (IND-7681) to FDA, and resulted in a notice of adverse findings dated 4/6/81.

Specific questions assigned for coverage by HFD-180 included:

1. Mitoxantrone (IND-16802) Failure to submit two toxicity reports to FDA.
2. Indicine-N-Oxide (IND-13952) Failure to report drug related deaths to FDA promptly.
3. Deoxycoformycin (IND-16505) Clinical studies initiated prior to sponsor (NCI) approval.
4. 5-Methyl (IND-18237) Clinical studies initiated prior to IND approval.

The inspection confirmed the validity of these deficiencies, and covered NCI's procedures for submitting alarming reports to FDA and their investigational drug distribution controls. NCI isiin the process of improving these procedures. Voluminous records on the referenced studies were copied for a detailed review by HFD-180. Additional computerized patient records will be submitted directly to HFD-180 when available.

FFU: Referred to HFD-180 for review of all data collected upon request. BLTeDO has not made additional copies and these records must be returned to BLT-DO upon completion of the review. Recommend notice of adverse findings regarding prior deficiencies and FDA/HFD-180 review of all new NCI procedures on investigational drug study monitoring.

#246

SIGNATURE John M. Dietrick
Supervisory Investigator

DATE: 9/21/81

DISTRIBUTION: O: BLT-DO cc: HFD-180, WBT-RP, DFU, HFO-520

FORM FDA 481(E)-CG (10/79)

DATE ASSIGNED: 7 /81 PRIORITY: DATE INSPECTED: July 16-Sept.4, 1981

CENTRAL FILE NO.: 1119714 JD/TA: 13 PHONE: 301-496-5223 GRP:

NAME: NIH/NCI/Div.of Cancer Treatment STREET: NIH

CITY: Bethesda COUNTY: 031 STATE: Md. ZIP: 20205 DISTRICT:

RELATED FIRMS: HHS

REGISTRATION:

REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR
	/	/	/		/	/	/		/	/	/
	/	/	/		/	/	/		/	/	/

INDUSTRY CODES ON THE OEI: 60Z

TOTAL ESTAB. SIZE	I.S. BUSINESS RECEIVED	SOLD	PRINCIPAL EST TYPE	RECALL NO.	REFUSAL CODE
1	YES [✓ NO]	0 %	4		0

ESTAB.STATUS: CHANGES: [✓ NONE] NAME ADDRESS OWNERSHIP SIZE PROD CODE EST TYPE
OTHER: NEW FIRM O/B INACTIVE NOT OEI REGISTRATION

PAC	PROCESS (PRODUCT) CODE	EST TYPE	~~ANN VAL~~	EMPL1 PC: 2 NO: 321 HD: 2	EMPL2 PC: NO: HD:	EMPL3 PC: NO: HD:	PRODUCT	PRITY	RESC HFD DATE	CLASS	D.O. CONC
48810	60Z	4	1	252			IND's	2	N/S	5	-

RECEIVED
SEP 24 1981
HFD-160
BUREAU OF DRUGS

SAMPLES COLLECTED: None
SAMPLE: PRODUCT:

FOR CONVEY/SUPPORT FACIL INSP

TOTAL	# VAI	# OAI

HEADQUARTERS UNIT REFERRED: HFD-180

FD 483 ISSUED: YES [✓ NO]

REASON REFERRED CP 7348.810/TWX 7/15/81

OTHER FED GOVT/INSP OR GRADING: non

INSPECTOR'S NAME/SIGNATURE:
Laurie S. Meade Jr Gurston Turner
Laurie S.Meade,Jr.321/Gurston Turner,HFD-180

SUPERVISOR'S NAME/SIGNATURE:

FORM FD 481(A)-CG (10/79)

PRODUCTS LISTED/COVERED

CFN: 1119714 EMPL NO.: 321

ESTABLISHMENT NAME: NIH/NCI/Div.of Cancer Treatment

DATE INSPECTED: July 16-Sept 4,1981 DATE ASSIGNED : 7 /81

DATE COVERED	PRODUCT CODE	EST TYP	EST TYP	EST TYP	PRODUCT DESCRIPTION
7/16 / 81	60Z——	4			DHAD
7/16/ 81	60Z——	4 4			Indicine-N-Oxide
7/16/ 81	60Z---	4			DCF
7/16 /81	60Z——	4			5-Methyltetrahydrohomofolate
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FORM FDA 481(C)-CG (10/80)

EIR: NIH/NCI/DCT
Bethesda, MD 20205 7/16-9/4/81 LSM/GT

SUMMARY OF FINDINGS

This "directed" inspection of the National Cancer Institute, Division of Cancer Treatment was prompted by HFD-180 telecom/TWX of 7/15/81 to BLT-DO from Gurston Turner, Ph. D., Pharmacologist. HFD-180 had learned of possible violations of IND regulations involving several oncolytic drugs sponsored by this Government agency.

The investigational drugs involved and suspected irregularities were:

1. Mitoxantrone (DHAD), IND-16802 — Failure to submit to FDA two non-clinical laboratory studies showing cardiotoxicity in white rabbits.

2. Indicine-N-Oxide, IND-13952 — Failure to promptly report suspected drug-related deaths to FDA.

3. Deoxycoformycin (DCF), IND-16505 — Administered to humans by clinical investigators at M.D. Anderson Hospital, Houston, Texas prior to sponsor (NCI) approval of the protocol.

4. 5-Methyltetrahydrohomofolate (radiolabeled), IND-18237 — Administered to humans at M.D. Anderson Hospital prior to IND approval.

This inspection included interviews with several DCT officials, and the review of voluminous records on file at the Cancer Therapy Evaluation Program, and Developmental Therapeutics Program of DCT.

Aside from determining the validity of the reported irregularities, the current inspectional approach was to review all available records pertaining to the four drugs with emphasis on preclinical toxicity studies, and reporting and monitoring of adverse reactions of Phase I studies. Numerous documents were copied for a detailed review by appropriate Bureau of Drugs officials.

This inspection confirmed that two toxicity studies on white rabbits, one using Adriamycin analog NSC #299195, dated 8/20/79, and the other, analog NSC #287513, dated 1/7/79, were not submitted to FDA as part of IND-16802 application. Both reports were on file in the DCT's Investigational Drug Branch, the office directly responsible for IND submissions. The reports were received By IDB on or about 9/26/80, and 11/14/80, respectively.

As for drug-related fatalities (hepatotoxicity) following administration of Indicine-N-Oxide in Phase I trials, this inspection confirmed that NCI was made aware of similar drug-related deaths prior to 6/16/80, but did not formally report such incidents to FDA until 5/5/81 (telephone).

All available documents pertaining to the two incidents at M.D. Anderson Hospital, and follow-up actions taken by NCI were copied as exhibits.

Supplementary areas of interest to HFD-180 covered during this inspection were:

1. Documentation of all protocols in use by and all investigational drug shipments since 1976 to Stephen E. Jones, M.D., Clinical Investigator.

2. Submission of pre-clinical histopathology results to FDA.

3. Additional information related to the FDA's investigation of Marc Straus, M.D., Clinical Investigator.

Less familiar abreviations used in this report are:

DCT - Division of Cancer Treatment
IDB - Investigational Drug Branch
DTP - Developmental Therapeutics Program
CTEP - Cancer Therapy Evaluation Program
CIB - Clinical Investigations Branch
DHAD - Dihydroxyanthracenedione (Mitoxantrone)
5-Methyl - 5-Methyltetrahydrohomofolate

Exhibits are cross-referenced in the following narrative where applicable. See the heading Exhibits at the end of narrative report for the order of attachment.

Computerized patient data was not available during the inspection. It will be obtained from IDB when it becomes available from the contractor.

PERSONS INTERVIEWED AND RESPONSIBILITY

Arrangements for this inspection were made by HFD-180. On 7/16/81 we visited the Investigational Drug Branch of the Division of Cancer Treatment where credentials were displayed and Notice of Inspection was issued to Daniel F. Hoth, M.D., Chief, IDB, the newly designated contact-person between FDA and NCI. In his position as Chief, IDB, Dr. Hoth's office is responsible for liaison with FDA, to include preparation and submission of IND applications. Dr. Hoth arranged for the review of records on file in his branch, and was the official spokesman for the DCT. Dr. Hoth has held this position since January 1981 when he took over from Dr. Vincent Bono.

Others providing information and/or records to review from the IDB were:

John S. Penta, Ph. D., Head, Drug Regulatory Affairs Section — Up to the time of this inspection, Dr. Penta was the signatory of submissions to FDA. However, he resigned shortly after the inspection began.

Silvia Marsoni, M.D., Head, Drug Evaluation and Reporting Section — She provided information and records covering adverse reactions, and monitoring thereof.

David Abraham, Ph. D., Staff Member — Provided records for review.

D. Dale Shoemaker, Ph. D., Staff Member — He will replace Dr. Penta as Acting Head, Drug Regulatory Affairs Section. Although he did not actively participate in the inspection, he was present for the final discussion with Dr. Hoth and others.

Paul J. Vilk, Pharmacist — Provided protocol-clinical investigator identification and correlation, and computer printouts of requested drug shipments.

Non-members of IDB who were interviewed or provided inspectional assistance were:

Daniel Kisner, M.D., Deputy Director, Cancer Therapy Evaluation Program — Provided for the use of copying equipment.

Edwin M. Jacobs, M.D., Associate Chief, Clinical Investigations Branch. Dr. Jacobs was interviewed to determine if he was aware of additional information or documents pertaining to Marc Straus, M.D., the subject of an FDA investigation.

Dr. Jacobs was not aware of any information or documents which had not already been obtained from other sources by Dr. Turner (HFD-180).

On 8/12/81 an initial visit was made to the Developmental Therapeutics Program, the branch of DCT responsible for management of pre-clinical toxicology studies of NCI sponsored drugs. The visit was pre-arranged with the below named responsible individual via telephone on 8/11/81. Credentials were displayed and Notice of Inspection was issued to John S. Driscoll, Ph.D., Acting Associate Director. Dr. Driscoll arranged for our review of his program's files dealing with the four investigational drugs in question. Others in DTP who were interviewed and/or provided records for review were:

John A.R. Mead, Ph.D., Deputy Director — Dr. Mead provided his copies of "Decision Network" files for our review and copying.

Michael C. Lowe, Ph.D., Acting Chief, Toxicology Branch — Dr. Lowe provided information regarding the submission of NCI-sponsored toxicology study reports to IDB for inclusion in IND submissions. Dr. Lowe was also issued a Notice of Inspection on 8/24/81.

Ruth D. Davis, Staff Member, Toxicology Branch — Ms. Davis also provided information regarding submission of toxicology reports. She maintains the log sheets listing the drugs, titles, and dates of the reports, and the date the reports are submitted to IDB.

Robert R. Engle, Ph.D., Head, Chemical Resources Section, PRB, DTP — Provided documentation of the shipment of radiolabeled 5-Methyltetrahydrohomofolate to Dr. Ti Li Loo at M.D. Anderson Hospital.

Paul Davignon, Chief, Pharmaceutical Resources Branch, and Bill New, Administrative Officer, DTP were present for the final discussions with Dr. Driscoll.

An organizational chart for the Division of Cancer Treatment is attached as Exhibit #1.

The inspection team was composed of Laurie S. Meade, Jr., Investigator, Falls Church R.P. and Gurston Turner, Ph.D., HFD-180. John M. Dietrick, Supervisory Investigator, participated in one inspectional visit on 8/24/81 to DTP.

On-site inspectional visits were made on the dates indicated below to two different locations. The Cancer Therapy Evaluation Program and its elements, to include the IDB, are housed in the Landow Building, 7910 Woodmont Ave., Bethesda, MD. The Developmental Therapeutics Program is located in the Blair Building, 8300 Colesville Rd., Silver Spring, MD.

IDB	DTP
July 16, 24 (Turner), 29, 30, 31 (Meade)	August 12, 14, 17, & 18 (Meade), 24 (Meade/Districk), 26 (Meade)
August 6, 10 (Meade), 12	
Sept. 4	Sept. 3

OPERATIONAL HISTORY

The initial inspection of this Government sponsor of investigational drugs was initiated in July 1979 as a follow-up to reports that the Division of Cancer Treatment failed to promptly report severe adverse reactions and deaths related to Methyl-CCNU (IND-7681). After multiple FDA District inspections made as a follow-up to the July 1979 inspection, a Notice of Adverse Findings letter issued 4/6/81 to Dr. Vincent T. DeVita, Director, NCI.

The only major change in responsible personnel since the July 1979 inspection has been the replacement of Vincent Bono, M.D., by Daniel F. Hoth, M.D., in January 1981, as Chief, Investigational Drug Branch — the designated liaison office with FDA concerning IND submissions. John S. Penta, Ph.D., Head, Drug Regulatory Affairs Section, resigned during the course of this inspection. Organizational charts for DCT and IDB are attached as Exhibit #1. Also, since the previous inspection, the IDB has moved from the NIH Campus to the Landow Building, 7910 Woodmont Ave., Bethesda, MD. However, the mailing address remains the same.

An operational procedures manual, outlining the handling and monitoring of clinical trials by DCT, was obtained as an exhibit during the July 1979 inspection. Sections dealing with the monitoring and reporting of adverse reactions are undergoing revisions at this time. Exhibit #2 of this report consists of two reports which explain the drug development program with emphasis on the pre-clinical and decision network processes prior to clinical trials. Exhibit #4 is a copy of "Evolution of the National Cancer Institute Master Plan for Drug Development and Interactions with the Food and Drug Administration", dated 5/15/81.

Exhibit #5 is a memo, dated 7/14/81, from John S. Macdonald, M.D., Associate Director, CTEP dealing with possible changes in the manner in which names of clinical investigators in Phase I studies are reported to FDA.

MITOXANTRONE (DHAD) — IND-16802

By letter, dated 6/17/81 (Exhibit 74) NCI reported four cases of cardiotoxicity to FDA. A telephone call on 7/7/81 to FDA reported two more adverse reactions. By the time a follow-up letter was issued to FDA, 7/15/81, (Exhibit 69A) a total of nine cases of cardiotoxicity had been reported including five deaths.

This inspection verified that two pre-clinical toxicology reports, although on file at IDB, have not been submitted to FDA. Both test systems, New Zealand White Rabbits, exhibited toxicoses to include cardiotoxicity. Exhibit 100 is report #RSS-299195-1979-12, dated 8/20/79, an Adriamycin Cardiotoxicity study comparing Anthracenedione Dihydroxy-diacetate, analog NSC #299195. Records (Exhibit 110) on file at DTP shows this report was transmitted to IDB on 9/26/80. A second report (Exhibit 107), #RSS-287513-1979-07 dated 1/7/79, was transmitted to IDB on 11/14/80 (Exhibit 114).

INDICINE-N-OXIDE — IND-13952

As of 7/13/81 there have been seventeen reported cases of hepatotoxicity including ten possibly-related drug deaths (Exhibits 23/24). From a review of records and interviews with NCI personnel, NCI first notified FDA of hepatotoxicity via telephone on 5/5/81. Formal written notification was via letter dated 7/13/81, Exhibit 24.

An internal IDB memo dated 6/16/80 (Exhibit 42) reveals they were aware of two fatal hepatotoxicities at the Mayo Clinic. However, we could not locate any documentation that NCI reported these adverse reactions to FDA. "Minutes of the Phase

I Working Group", dated 11/28/79, (Exhibit 44) also indicates possible evidence of hepatotoxicity. A letter, dated 5/12/81 (Exhibit 28) from John S. Kovach, M.D. of the Mayo Clinic, to Dr. Hoth, IDB, points out that he (Kovach) reported "5 patients with severe hepatotoxicity" in the New Drug Liaison Group meeting of 10/1/80.

DEOXYCOFORMYCIN (DCF)— IND-16505

By letter, dated 6/19/81, NCI notified FDA that Gerald Bodey, M.D., had initiated a clinical trial with DCT without the approval of NCI. The drug had been shipped for clinical use under another protocol approved by NCI. The actions taken by NCI included the temporary suspension of Dr. Bodey's FD-1573, the recall of DCF stocks, and the requirement that M.D. Anderson Hospital, Houston, Texas improve their drug accountability procedures. Exhibits 122 & 126, pertaining to this incident, are attached.

5-METHYLTETRAHYDROHOMOFOLATE — IND-18237

On 6/16/81 NCI notified FDA by letter that researchers at M.D. Anderson Hospital, Houston, Texas had administered radiolabeled 5-Methyl to four patients without IND or NCI approval. The drug had been shipped to Dr. Ti Li Loo for use in animals in April 1978. NCI learned of the human experiments through an article in a scientific journal. Records copied from IDB files pertaining to this incident are attached as Exhibits 15A thru 15E. NCI memos and the report covering their investigation of this incident, obtained from Dr. Hoth's office on 8/26/81, are attached as Exhibits 14A & 14B.

The radiolabeled drug was shipped on 4/26/78 by NCI-Contractor, SRI International, Menlo Park, Calif. Dr. Robert R. Engle, Head, Chemical Resources Section, DTP, provided the documents in his possession pertaining to the drug shipment and labeling (Exhibits 17A & 17B).

STEPHEN E. JONES, M.D., CLINICAL INVESTIGATOR

IDB was requested to provide a list of all protocols used by, and all drug shipments, since 1976, to Stephen E. Jones, M.D.

Paul Vilk, Pharmacist, supplied the requested information via computer printouts attached as Exhibits 6A & 6B, respectively.

DISCUSSIONS WITH MANAGEMENT

At the initiation of the inspection on 7/16/81, Dr. Daniel Hoth, Chief, IDB was informed of the reasons for this inspection. Specifically, it was pointed out to Dr. Hoth that we were interested in adverse reactions and deaths associated with DHAD and Indicine-N-Oxide, submission of toxicology reports to FDA relating to DHAD, and the use of DCF and 5-methyl in humans at M.D. Anderson Hospital prior to protocol and/or IND approvals. Dr. Hoth was informed that we would make a complete inspection by reviewing all available records covering these four drugs. Subsequently, Dr. Hoth was requested to provide "all" records and files pertaining to the four drugs.

Additional requests made to Dr. Hoth during the initial meeting on 7/16/81 included inquiry into why pre-clinical histopathology results for tricylicnucleotides (IND-18905) had not been submitted to FDA prior to Phase I trials. Dr. Hoth commented he did not think such as inquiry was appropriate for an inspection since by joint agreement NCI would submit histopathology during Phase I and prior to Phase II. Dr. Hoth expressed concern that we were on a "fishing expedition" — apparently because he was not familiar with FDA inspections. We then discussed FDA inspectional authority and procedures. On 7/24/81 Dr. Kisner, Deputy Director, CTEP also expressed to Dr. Turner that our "fishing expedition" was needlessly tying up his staff with our requests.

Present for the final discussions at IDB on 9/4/81 were Drs. Hoth, Kisner, Marsoni, and Shoemaker. The major inspectional observations pointed out were the failure to submit two previously identified pre-clinical toxicology studies with the IND for DHAD, and the late reporting of adverse reactions and deaths associated with Indicine-N-Oxide. Dr. Hoth acknowledged the validity of our observations, and commented he would make rectifications to prevent such occurrences in the future.

We commented that NCI sponsored drugs were being diverted for unauthorized use, citing the examples of DCF and 5-Methyl. We further offered our opinion that their filing system left much to be desired. For example, we could not find a Decision Network file at IDB documenting fully the material facts on which decisions were made. We suggested they establish one complete file for each drug rather than the present system in which several people in the branch maintain their own drug files.

Dr. Hoth commented they were in the process of revising procedures for receiving, monitoring, and reporting of adverse drug reactions. He said a meeting was planned for the following week with officials of the Bureau of Drugs to discuss problem areas such as this. Before terminating our discussion with Dr. Hoth, we pointed out that our observations were preliminary in nature, that other observations may be forthcoming after the large volume of copied material is reviewed by the Bureau.

One category of records, specific patient data, requested at the beginning of the inspection was not available. The information has to be obtained from a private computer contractor, and will probably take several weeks. Dr. Marsoni, who was assigned the task by Dr. Hoth, will submit the material by mail when it becomes available.

On 9/3/81 a final discussion to clarify questions relating to toxicology reports was held with personnel at DTP. Present for this meeting were Drs. Driscoll, Mead, and Lowe, Ms. Davis, Mr. Davignon, and Mr. New. Also present at this meeting was Mr. Jim Michie, of the U.S. Senate Subcommittee on Investigation and General Oversite. Mr. Michie is also conducting an investigation of NCI (See Exhibit 116B).

Dr. Lowe commented he was responsible for submitting all NCI sponsored toxicology reports, including compound analogs, to IDB. He pointed out that such compounds as DCF and DHAD were originally commercially sponsored drugs, and, therefore, NCI would not have contracted the pre-clinical toxicology studies.

Ms. Davis clarified the length of time between the actual report dates and dates of submission to IDB. The dates the reports are received from the contractors are stamped on the back cover of the reports. The time difference is usually several months. Ms. Davis's system of recording the submission dates of reports to IDB is a loose leaf notebook in which she originally intended to record dates in green pencil or pen to note submissions. However, she pointed out the green markings are not that significant since the only purpose of the log is recording of toxicology reports submitted to IDB. However, since our inspection the toxicology branch has devised a transmittal form (Exhibit 3) to be returned by IDB upon the receipt of reports.

As for clarification of whether or not a report (Exhibit 161B) on the pharmacology of drug combinations involving DCF was submitted to IDB, Dr. Lowe stated the study was not managed by the toxicology branch because it involved drug combinations and would have been handled by the Chemical Pharmacology Branch under Dr. Adamson. Dr. Mead stated he specifically remembered sending the report, dated 5/31/79, to Dr. Penta in IDB because he attended a meeting around that time with Dr. Penta and Parke-Davis representatives. However, documentation of these facts were not readily available.

EXHIBITS

Documents obtained during this inspection are numbered as Exhibits 1 thru 162 — some with subparts A, B, C, etc. The total number of pages is approximately 2,063. Where possible all exhibits pertaining to a particular drug are bound in one folder, and generally arranged in ascending order by dates, if dated. Exhibits 1 thru 12 relate to general procedures, two or more of the four drugs covered during the inspection, or to other drug categories. The following is a list by exhibit number, indicating from where obtained, and the specific topic or drug covered.

Number	Topic	Source
1	Organizational Chart	IDB
2	General	DTP
3	Toxicology Reports	DTP
4	Master Plan for Drug Development	IDB
5	Names of Phase I Investigators	IDB
6	Stephen E. Jones, M.D.	IDB
7	Protocols, and Drug Shipments	IDB
8	Decision Network Agenda General	Dr. Mead & DTP
9-12	General	IDB
13	Decision Network 5-Methyl	Dr. Mead
14-16	5-Methyl	IDB
17-18	5-Methyl	DTP

Number	Topic	Source
19	Decision Network Indicine-N-Oxide	Dr. Meade
20-58	Indicine-N-Oxide	IDB
59-62	Indicine-N-Oxide	DTP
63	Decision Network DHAD & Analogs	Dr. Mead
64-109	DHAD & Analogs	IDB
110-118	DHAD & Analogs	DTP
119	Decision Network DCF	Dr. Mead
120-160	DCF	IDB
161-162	DCF	DTP

Laurie S. Meade G

Laurie S. Meade, Jr., 321
Investigator
Washington Resident Post

Gurston Turner, Ph. D.
Pharmacologist, HFD-180

LSM/GT/sls: 9/18/81

Senator HAWKINS. Do you have a list of recommendations for us?

Mr. MEADE. In my position, I would have to say "No." I would prefer recommendations come from someone higher up in my agency rather than me sticking my neck out. It is not one of my normal job functions to make recommendations.

Senator HAWKINS. Thank you. We want you to keep up the good work, Mr. Meade. I have been cautioned that some of you may become known as whistle blowers.

Dr. Young, you are the medical review officer in the Division of Oncology and Radiopharmaceutical Drug Products. Prior to joining FDA in 1975, you were a physician employed in the NCI's drug development program; is that right?

Dr. YOUNG. Yes, madam.

Senator HAWKINS. And I understand that you are the medical officer responsible for monitoring experimental use of the drug DCF; is that right?

Dr. YOUNG. Yes, madam.

Senator HAWKINS. We have 7 minutes to vote again. When I return, would you give us a brief status report on the use of DCF, and tell us whether there have been problems associated with its use in clinical trial?

I will be back in 5 minutes.

[Whereupon, a brief recess was taken.]

Senator HAWKINS. Back on the record.

Dr. Young, could you tell us about the status report on the experimental drug, DCF?

Dr. YOUNG. Madam Chairman, the drug DCF could be thought of as a microcosm of the universe that is NCI. It has a little bit of all the management problems. This drug was put into clinical trial in June of 1979. Its first annual report was delivered to us last week, after quite a bit of prodding on the part of the FDA to get the drug report in to us.

[Information supplied for the record follows:]

PROGRESS REPO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20205

October 16, 1981

IND 16505
NSC 218321
2'Deoxycoformycin

Food and Drug Administration
Bureau of Drugs, HFD-150
ATTN: Document Control Room 17B34
5600 Fishers Lane
Rockville, MD 20857

Gentlemen:

Enclosed are three copies of the annual report for 2'deoxycoformycin (IND 16505, NSC 218321).

Sincerely yours,

National Cancer Institute
(Sponsor)

Per: Daniel Hoth /gm
Daniel F. Hoth, M.D.
Chief, Investigational Drug Branch
Cancer Therapy Evaluation Program

Enclosure

RECEIVED
OCT 19 1981
HFD-150
BUREAU OF DRUGS

(Note: In the interest of economy, the text of the annual report was retained in the files of the committee where it may be researched upon request.)

Dr. **Young**. The phase I trial, that is, the initial phase I trial, has been suspended voluntarily by the Cancer Institute. They report that out of the 110 patient subjects involved in that study, there were 20 possible drug-caused deaths. The study was conducted over a period of approximately 18 months, having been called off in about February of this year, and it was conducted at six institutions.

Now, in January of this year, 1981, the Cancer Institute submitted proposals for study of two drugs together, one of which was DCF, and the other was a drug, Ara-A. In that submission, that proposal for clinical trial of the combination, the Cancer Institute submitted no information on the DCF deaths; and I would presume that the 20 deaths had already occurred at or before the time that that proposal, the two-drug study, was submitted (January 1981).

Senator **Hawkins**. You said 20 deaths?

Dr. **Young**. Yes. The point I am trying to make is that maybe nobody at NCI is analyzing the data.

If I might continue——

Senator **Hawkins**. Surely.

Dr. **Young**. I think DCF studied as a single drug raises two problems. The first problem is really preclinical; that is, before the drug is put into trial, and that is whether there is sufficient animal data in order to put it in to trial. DCF came in with animal studies where the animals were dosed for a maximum of 5 days. In the human trial, there was essentially no limit to the time over which or the number of doses that the human subjects could receive of this particular drug.

The clinical problem is the problem of excessive deaths. In January of 1980, the FDA wrote a letter to NCI and alerted it to the fact that we had a report of kidney and brain problems associated with DCF that were not previously described. The NCI met that month, the same month that we sent the letter, in January of 1980, and brought in the institutions that were doing their initial study. Among other things, Sloan-Kettering reported that in one segment of its study, three of the seven patients that were on the study died as a result of the drug. M. D. Anderson reported that three to four out of eight of its patients on one segment of the study died because of the drug. And M. D. Anderson, as far as I can reconstruct from the record—I put a caveat in this in that FDA does not get very good data submission in terms of information from NCI—it appears that in this particular segment of the M. D. Anderson study, two patients got a total dose of 20, and both patients died—one, I would say definitely from the drug; the other, possibly from the drug. They went up—that is, they escalated the dose—they went up in the amount that they gave to a total dose of 40, and one of those two patients died. And in spite of that, they entered one more patient in at a total dose of 160, which is eight times the dose that killed at least one out of the two patients at 20, and four times the dose that killed, again, one out of two patients. And of course, that patient died from the drug.

Well, that was all reported to NCI by January of 1980, and then there was yet another year of studies of this drug. And in that year, we apparently accumulated another 12 to 14 more deaths possibly related to the administration of this drug. And the question that this raises in my mind, in terms of management and coordination of the study, is whether there was some failure in January of 1980, a year and a half ago, to recognize what was going on, or to analyze the data; and two, whether there is some kind of failure in disseminating this information; that is, coordinating the six institutions doing this study. I mean, they were in Boston, New York, Chicago, Houston. They are scattered essentially across the country.

Senator HAWKINS. What are the others? There were six?

Dr. YOUNG. Yes, six institutions. One was Ohio State. I cannot—it slips me what the last institution was—but essentially, they were just scattered across our country.

Well, the failure to disseminate and coordinate arises in this way. If NCI recognized the toxicity—I mean, these deaths that happened, three out of seven at Sloan Kettering, and three to four out of eight at M. D. Anderson—did they analyze it as to what was going on; and then, if they understood what was going on, did they disseminate that information? I cannot find in our records; that is, at the FDA, any kind of report that highlights the problem, the deaths, the unexpected deaths, actually, as described by Sloan Kettering. I do not find any advisory to the investigators, far flung, essentially across the country. And then, in January of this year, when the proposed study of two drugs together, one of which is Ara-A and one of which is DCF, is submitted there is no section describing what they have learned, if they have learned anything, on DCF—that is, what caused the deaths of these 20 out of 100 patients?

Senator HAWKINS. Did you encounter any problems with FDI and the NCI upper management contradicting the findings of physicians?

Dr. YOUNG. Well, this report only came in after much prodding. Maybe I should just give you the time frame of what happened. When the two-drug study was presented to us in January of this year, we said, "Well, wait a minute. We have heard a little bit about some unexpected deaths with the drug DCF. The question is how can NCI propose study of both these drugs together without telling us more about what has really happened with DCF?"

So we—not we, but Dr. Finkel, actually, our Associate Director—called NCI herself and said, "What happened? Give us a report. We would like to know. Here, you are proposing two drugs together, and we do not know what happened with just one drug (DCF) alone."

I do not know how to explain it. I guess nothing happened—meaning we did not get any report as to what happended; we did not get any feedback. And I think maybe in informal conversations, people may have raised the question: Where is the report? But formally, a letter went out in August of 1981 in which the FDA, I guess as an institution, said, "Remember our telephone conversation of February? We are still interested in the deaths that are associated with DCF. Where is the report?"

Well, no report came in, and in the beginning of October of this year, we informally called NCI and said, "Did we miss it? Maybe it came in and we did not see it."

But they said, "No, the report has not been submitted. We are trying to get this information back from the hospitals." Well, we finally got it last week. So I do not know what top management of NCI, or how they see this particular problem. I mean, we have just essentially gotten it, and it comes back as a report, I guess, without editorial comment as to how they see it.

They admit that the kidney toxicity is unexpected. I mean, I guess nobody expected it. It may be that there were not sufficient animal studies to highlight this particular problem. That is the preclinical problem that I brought up. I teach pharmacology, and I try to teach the students that drugs do not have just one action. They have many actions, and you have to be aware that there are many actions of drugs. And as you raise the dose, you kind of bring out what the different actions are, and the animal studies really have to reflect that kind of testing, because that is what you are going to do in human beings, and that is apparently what was done in the clinical trials with DCF.

Senator HAWKINS. Could you tell us what you think is needed now, at both FDA and the NCI, in order to improve the operation of these programs and to insure the safety of patients that are in cancer therapy?

Dr. YOUNG. I brought with me a copy of the Food, Drug, and Cosmetic Act, which was what you, as our elected leaders, believed, I guess, was a fair and reasonable baseline, standard of performance, minimum performance standard. And we supplemented that with our regulations. It is not this whole book. It is only a few pages. I do not think that the regulations are that onerous. I think that a careful investigator, in the course of his development of his study and conducting his study, will comply with our regulations.

I think what we should do is implement the regulations. Implement the law as it is written, and we should do it equitably; that is, across the board. There should not be any special arrangement, special favors. I think there is some, how should I say, protection in the fact that everyone gets treated the same, rather than we treat certain people differently. That would be my suggestion.

Senator HAWKINS. Thank you, Dr. Young.

[The prepared statement of Dr. Young follows:]

STATEMENT

BY

ROBERT S. K. YOUNG, M.D., Ph.D.

U. S. FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND GENERAL OVERSIGHT

COMMITTEE ON LABOR AND HUMAN RESOURCES

U.S. SENATE

WASHINGTON, D.C.

November 3, 1981

Madam Chairman,

Members of the Committee,

I thank you for inviting me to share with you my concern for the human subjects of the National Cancer Institute's clinical anticancer drug experiments. As a medical scientist monitoring the Cancer Institute's clinical research over the past six years, I have become increasingly suspicious of the way in which the Institute has managed its program responsibilities. From my outpost at the Food and Drug Administration, it appears that the Cancer Institute has consistently fostered a research environment in which the rights of human research subjects are not fully respected. It may be that cancer researchers are unconsciously taking advantage of the vulnerability of cancer victims and "misleading" them into taking experimental drugs, and the Institute has failed to adequately manage its research program. Since the FDA does not effectively monitor the Cancer Institute, diligent congressional oversight is both appropriate and critical to the protection of these research subjects. The "self-serving" statements of cancer researchers alone will no longer do. The recent Washington Post series on the "War On Cancer" has reinforced my suspicions, and has heightened my concern.

I am Robert S. K. Young, an employee of the U.S. Food and Drug Administration, which celebrates this year its 75th birthday as a consumer protection agency. I am currently a reviewing medical officer in the area of anticancer drugs, and have worked at the FDA for seven years. I am trained and have worked as both a research scientist and physician. The testimony I will present is not the "official" position of FDA management.

I welcome this opportunity to begin an exploration of issues raised by the recent series on the "War on Cancer". It is reassuring to those concerned with the rights of cancer victims to see that both houses of the Congress have initiated investigations, and are holding public hearings on how the War is being conducted. I assure you that there are more than enough serious and significant issues deserving of considered probing for both houses of the Congress. The American people have generously supported the War On Cancer by paying for it both monetarily and personally by "donating" their bodies to science. They have a right to know how the War is being conducted.

Although I welcome your investigation, my appearance before you is an admission of failure. Failure on the part of the clinical cancer research community to responsibly and authoritatively deal with those issues raised by the Post's series. Perhaps if I had articulated more clearly my misgivings concerning these same issues, Mr. Gup and Mr. Neumann could never have written their articles, and I would not find myself in this unfamiliar forum.

The series has apparently outraged two groups of people - the experimenters and those experimented upon. I will only discuss my concerns for the latter.

My analysis begins with a fundamental and seemingly simple question of public policy which you as our elected leaders are well qualified to respond to, and about which doctors have no special qualifications:

Is the cancer patient who serves as a research subject a human being? I start here because of the primacy of this question. Above all else clinical research should be humane.

Violations of the consequences that follow from an affirmative answer to this question is what has led to the outpouring of feelings in reaction to the Post's series. The articles describe matters unfortunately well within the common knowledge and experience of laymen. The primary consequence of an affirmative answer is that the cancer patient has rights which must be respected by others. The basic right in question is the integrity of his body despite the fact that it has been victimized by cancer. Without one's consent, offensive touching, let alone bodily harm by others is prohibited. There are two central issues then that I wish to explore:

1. The consent itself.
2 The scope of the consent.

Patients give valid consent only when they are sufficiently informed so that they can make a knowing and intelligent decision as to whether or not to participate in a clinical experiment, such as a phase I study. They have a right to self determination - to intelligently chart their own destiny with dignity. It appears that some patients are insufficiently informed in the following areas:

1. They do not understand the remoteness of personal therapeutic benefit.
2. They do not understand the substantial certainty and magnitude of the toxic effects.
3. They do not understand that they are "guinea pigs" "donating" their bodies to science.
4. They fail to realize that the experiments in which their participation is sought are experiments that their doctors would themselves decline to participate in if they were in the same situation.

Since this important area of inquiry is not within the scope of my expertise or most physicians, I leave its exploration to bioethicists. Besides the problems which have been raised, a discussion of the voluntary aspects of consent might also be most appropriate.

The second crucial area that might be explored is the scope of the consent obtained. To how much bodily harm do patient-subjects consent? As much as necessary; but not to unnecessary injury or unreasonable risks of harm? What is unreasonable? Let me suggest a guide which you initiated and authored - The Food, Drug and Cosmetic Act and its resulting rules and regulations. Together these set prophylactic minimum standards to forestall unnecessary injury. There are at least two scientific problems with NCI clinical cancer research:

1. Insufficiency of animal testing to define the toxic effects of drugs before they are administered to human beings.
2. Insufficient central management of the human experiments:
   -failure to scientifically define endpoints so that a drug that is not worth pursuing because it lacks efficacy, or is too toxic can be more quickly identified.
   -failure to analyze reported data.
   -failure to coordinate sets of studies.

The Post's series seems to be a tale of what human subjects have always wanted to know about clinical cancer research, but were too afraid to ask. The experimenters say, "Trust us." Those experimented upon are no longer sure that they should. Although everyone desires the discovery of a nontoxic cure for cancer, few seem willing to wage the War at any price, especially when their bodies are to be used as ammunition.

The staff of the FDA has been interested for more than a few years in some of the problems which are now being explored. Because they have not been satisfactorily addressed and resolved, however, it is little consolation to us that these problems were identified so long ago. In order to give the committee some insight as to the scope of the issues, I will, through documents highlight three of them:

1. Ethical issues, including informed consent.
2. FDA oversight of the Cancer Institute.
3. NCI program management.

My involvement with the NCI began in the summer of 1975 when I was transferrred to the Oncology Group of FDA.

ETHICAL ISSUES. A general exploration of the area of valid consent formally began with letters that were sent on November 4, 1975 to a number of persons known to have a particular interest in the area (Exhibit 1). After giving a brief description of the problem, the following questions were raised:

> "1. Does the representation of the experimental vs therapeutic aspects of the investigative trial (putative anticancer drugs in cancer patients) offer a potential situation in which a subject can be unfairly misled in terms of expected personal benefit?
>
> "2. If a misleading situation can be envisaged, how would you characterize it?
>
> "3. How can the danger of misrepresentation, if it exists, be minimized?"

I received a number of replies including some from experts in the field of bioethics (Exhibits 2 and 3). For a variety of reasons, I was never able to effect any real change in this area.

Not everyone at the FDA or the NCI considered an interest in the ethical and public policy aspects of clinical cancer research as particularly germane to medical scientists, and some tried to reframe public policy questions as purely technical issues . For example, Vincent T. DeVita, Jr., M.D., then Director of the Division of Cancer Treatment (NCI) wrote me on November 15, 1976:

> "It seems to me in our discussions you have devoted most of your time to the ethics of drug development rather than the scientific content. Perhaps, as you suggest, they are so intimately intertwined that devoting all your attention to one or the other will accomplish the same goal. I doubt it." (Exhibit 4)

More recently (March 31, 1981) J. Richard Crout, M.D., Director of the Bureau of Drugs wrote:

> "I have not seen Dr. Young's communications to the President's (Bioethics) Commission. I would assume, however, that he frames the issues in ethical terms and deals with them philosophically...The controversy, in my judgement, is largely one of defining the best technical approach to identifying potential human risks in the evaluation of anticancer drugs." (Exhibit 5)

In a July 9, 1981 memorandum Dr. Crout describes one of NCI's basic technical principles:

> "For such drugs NCI feels that there is no toxicity (except perhaps serious irreversible organ damage) that would preclude Phase I testing in humans...This basic tenet of the NCI approach - that essentially all drugs that pass a screening program for efficacy should be tested in humans is a startling concept to many of

us...Much of the controversy over the new NCI toxicology guidelines results, in my judgment, from whether one accepts this basic tenet of the cancer drug development community." (Exhibit 6, page 3) Whether the public accepts this NCI tenent as a narrow technical issue to be left solely to the discretion of scientists, or as a public policy issue deserving of general discussion is an open question.

I have attached Dr. Le Roy Walters' article as an example of a concise discussion of some ethical issues in research involving human subjects (Exhibit 7).

FDA OVERSIGHT OF NCI. Some directors of the Bureau of Drugs seem to have an aversion to enforcement of the Food, Drug and Cosmetic Act and new drug regulations as they pertain to clinical investigators. In 1973, FDA's Scientific Investigations staff wanted to send letters pointing out deficiencies to sponsors and investigators who had been inspected under a 1972 special survey. The Director of the Bureau of Drugs doubted the legality of the proposed letter.

The HEW Assistant General Counsel, Food, Drugs, and Environmental Health Division, in his response to the Director's request for a legal determination, stated:

> "Contrary to your note of 10/23/73 attached to the file, I do not believe that the letter...is either harsh or an over-kill. Nor do I agree that it should be 'tempered' with equivocal statements. The investigators who receive letters like this are grown men. They must understand the importance of the work they are doing, and the fact that the law imposes obligations upon them...I see no more

reason to coddle the medical profession than I do to coddle drug manufacturers or food warehouse owners. Where criticism is deserved, it should be set forth in a candid and honest manner." (Exhibit 8)

Initial efforts to provide oversight of the NCI were relatively well received. In her October 30, 1975 memorandum to William Gyarfas, M.D., Director, Division of Oncology and Radiopharmaceutical Drug Products, Marion J. Finkel, M.D., Associate Director for New Drug Evaluation wrote:

"I wish to congratulate you on your efforts to bring NCI into full compliance with the IND regulations. If Dr. Slavik (NCI executive) fulfills his commitments, it will be a major accomplishment for HFD-150 (Division of Oncology and Radiopharmaceutical Drug Products)." (Exhibit 9)

On the next day, October 31, 1975, Dr. DeVita met with Dr. Crout to find out why the "administrative laxness" (Exhibit 10, page 2) that had previously existed appeared to be on the wane. At the end of a rather long discussion, I tried to summarize the issues by asking Dr. Crout, "Whether or not the NCI was going to be above the law?" After a short silence, someone suggested that that was not an issue. Actions, however, do speak louder than words, and the staff soon found out that NCI had a very "special arrangement" (Exhibit 10, page 1).

On February 2, 1976, Dr. Crout instructed the staff:

"No clinical hold will be placed on any such (NCI) IND, however, unless there is positive evidence in the application or elsewhere of lack of safety of the study or unless the application is grossly deficient in one or more of its sections..." (Exhibit 11)

This rule was promulgated even though in the same memorandum he observed:

> "The problem, as I understand it, is that the quality of the IND submissions from the NCI is such that, all too often, we in the FDA simply do not have the evidence upon which to make a valid determination of the safety of initial studies." (Exhibit 11)

How the staff was to find "positive evidence" of lack of safety in a submission that did not have the evidence upon which to make a valid determination of safety has never been fully explained.

On March 11, 1976, the top executives of the NIH, the NCI and the FDA met to discuss the new drug requirements. Among other things Commissioner Schmidt stated that:

> "What is at issue is FDA's ability to do its job. Part of that job is the review and approval of IND protocols. In order to accomplish this objective, certain information is needed whether it be from private industry or NCI. FDA can no longer operate on good faith in this area...if the NCI program is unique, these differences must be agreed upon by all concerned so that the differences are fully understood by everyone including the public at large." (Exhibit 12)

There was "agreement that the scientific and regulatory standards of FDA can be met by NCI and other cancer scientists without impeding the National Cancer Program." (Exhibit 13) Despite this agreement the rule restricting the imposition of clinical holds has never been rescinded.

> After one year (1976) in the cancer group of FDA, I recommended: "FDA should inspect the NCI, DCT operation to determine if the NCI as sponsor has the resources, dollars, people and material to adequately monitor and run its clinical investigational program." (Exhibit 14)

This inspection has never been conducted by FDA. To my best knowledge and belief and to its credit only the Senate's Investigations and General Oversight Subcommittee has ever made such an on site visit.

Groups outside the NCI have lobbied in support for no FDA oversight of the NCI. On December 3, 1976 the American Cancer Society wrote:

> "...the National Cancer Law extension in 1977 should provide, within the concept of technical amendments, for National Cancer Institute control over the testing of new anticancer drugs, instead of FDA control...It would seem that only legislation can tie down the point that cancer patients are different from others...In effect, the cancer patient near death is the best possible test medium, both from an ethical standpoint and from a scientific standpoint. Results in humans need not be interpolated to a different species, as do animal results." (Exhibit 15)

NCI Program Management. Because "administrative laxness" (Exhibit 10) had prevailed until the mid-1970's with regard to NCI, quick correction of problems was conceded to be impossible. On August 21, 1975, we asked, however, that the NCI initially concentrate its remedial activities in three areas:

"1. File an accurate progress report for each IND for which none have been submitted over the last year. For those INDs which have had annual reports filed in the last year, the National Cancer Institute, Cancer Therapy Evaluation is to establish that each report includes an "Outline of any phase or phases of the planned investigation." (See paragraph 10, Form FD 1571). In this connection, we include for clarity of communication:

> 'Websters Third New International Dictionary, 1971 defines the noun 'report' such as in the phrase 'annual report' as 'an analysis of operations and progress and a statement of future plans made at stated intervals by an administrator or executive to superiors or those to whom he is reponsible.'

"2. For each protocol accepted under an IND, the NCI must be sure and declare that the protocol conforms to guidelines in section 314.111 of the CFR (title 21), that the investigators are qualified by training and experience to conduct the trial, and that adequate facilities are available for care of the experimental subjects. The NCI as sponsor must also explain how the particular protocol in question fits into, or contributes to the plan of development of the drug.

"3. Submit a plan that will assure (that) the results of investigations are returned to the NCI for analysis." (Exhibit 16)

To this day we have not achieved all of the rather modest goals set out in this letter. To illustrate the problem in practical and concrete terms, I submit an outside group's analysis of difficulties encountered with a number of NCI drugs (Exhibit 17).

The regulatory problems that result from the NCI's failure to scientifically manage its clinical research program has been recognized at all levels of FDA. For example, Commissioner Kennedy on June 4, 1979 wrote:

> "Most (FDA) reviewers of this NDA (18-057) voiced their concern that the quality of data submitted--although adequate for approval--could have been much improved. I believe it is of the greatest importance that we receive the best possible scientific data for making necessary judgments about safety and efficacy, particularly on cancer drugs, which involve some of the most important and difficult decisions we have to make. I am asking that the Bureau upgrade and increase its efforts--referred to in Dr. Crout's December 18, 1978, memorandum--to solve this problem. If it is found that two-party negotiations are not providing the results anticipated, because of too great a difference in purpose or for other reasons, then we should pursue other avenues to achieving the desired results."
> (Exhibit 18)

On March 3, 1980, I resigned as supervisory medical officer in the area of anticancer drugs (Exhibit 19). Because I no longer exercise broad oversight in the area, I do not know how the Cancer Institute of late has been managing its program. With FDA approval, however, it currently adheres to a program of drug testing that in some phases largely substitutes humans for animals to determine the toxic effects of experimental drugs (Exhibits 20 and 21). I am somewhat skeptical of a program that would implement such a procedure.

In closing I wish to confine myself to two editorial comments:

1. Thank goodness we have a free press, and a coordinate branch of government that can conduct an independent assessment of problems and issues.

2. It's about time.

Madam chairman, members of the committee, I would be pleased to respond to questions that you or your committee might have.

(Note: In the interest of economy, the exhibits referred to were retained in the files of the committee where they may be researched upon request.)

Senator HAWKINS. Dr. Wood, like everyone else on the panel, you have an impressive background—8 years at the FDA, the past 5, you were a supervisory chemist in your division, 10 years in the chemical industry, and a professor of chemistry at the University of New York. And before we begin questioning you, I think it would be helpful to most of us if you would describe the role of the chemist in the review of investigational, new anti cancer drugs.

Dr. WOOD. Well, part of my responsibilities are to supervise a group of senior chemists in the review of new drug applications and investigational drug applications, involving not only cancer drugs, but also anti-inflammatory drugs, and radiopharmaceutical drugs. We have a very small staff of only six chemists to do this. They are responsible fully for drug quality and purity. And I am finding, perhaps, a little more difficulty recently in assuring that we get the best possible scientific review of data submitted in these applications.

I am a reluctant witness at the present time, but I feel it is my duty to bring out the current pressure that is being applied to compromise scientific reviews. I think the FDA needs the best possible scientists and the best possible review of data.

Senator KENNEDY. By whom?

Dr. WOOD. By the scientists with the FDA.

Senator KENNEDY. But who is asking you to compromise?

Dr. WOOD. I would say FDA management, under the guise of speeding up the review process. I think we all want to get good drugs out in the market, get them to patients as fast as we can, but there is more than one way to skin a cat, and that is not by compromising scientific reviews. We can speed up the processing of documents. We can speed up getting letters out to NCI and other firms involved. We can write guidelines to help them. All I am saying is there is extraordinary pressure at the present time to compromise scientific reviews; to force people to delete deficiencies; that is, information is essential for the establishment of good drug quality. And I think we are going to lose our scientific staff at the FDA if this continues.

Senator **Hawkins**. Dr. Wood, you heard earlier testimony today of this panel—by the way, everyone on this panel was subpenaed by this subcommittee, so when Dr. Wood said she was here reluctantly, that may be the feeling of everyone on this panel here today; we appreciate your coming, however—you have heard the other witnesses on this panel speak of pressures to stop an FDA inspection, reluctance of the NCI to cooperate, and upper management at FDA over-ruling decisions of its scientists and physicians.

I have a memo dated April 25, 1978, from the Assistant Associate Director for New Drug Evaluation to the Associate Director for New Drug Evaluation. The subject of the memo is "National Cancer Institute's IND's". Do you have a copy of that memo?

Dr. **Wood**. Yes, I do, Senator.

[The memo referred to follows:]

APR 25 1978

Associate Director for New Drug Evaluation
(HFD-100)

To: Dr. Wood

Assistant Associate Director for
New Drug Evaluation (Chemistry)
(HFD-102)
National Cancer Institute's IND's

Reference is made to the April 13, 1978 letter to Dr. J. Richard Crout from Dr. Vincent T. DeVita (NCI) in regard to FDA requests for additional manufacturing and controls information for NCI's IND's.

As you recall, the concern of the Bureau Director was communicated to you by telephone a few weeks ago. At that time you informed me of this concern. I contacted the Supervisory Chemist, Dr. R. Wood (HFD-150), and discussed with her the concern of "over requesting" information and data that NCI had brought up for drugs in the investigational stage. I instructed her that in order to help avoid any future problems that all communication with NCI, in regard to manufacturing and controls for IND's, should be reviewed with me before they are finalized. In carrying out this procedure, we would be in a better position to justify any requests to NCI. If a meeting seemed appropriate to discuss differences, we would arrange for such a meeting.

The two letters (concerning IND 13,950 and IND 13,953), dated March 10, 1978 and March 13, 1978, that were attached to Dr. DeVita's letter were sent out before my discussion with Dr. Wood. Likewise our arrangement with Dr. Wood was made prior to the date on Dr. DeVita's letter.

I will review the two IND letters and discuss them with Dr. Wood. Any changes in the requests, for this stage of the investigations, will be communicated to NCI.

Charles S. Kumkumian, Ph.D.

cc: HFD-1
HFD-100
HFD-102
✓HFD-150
HFA-224

Rec: 2/26/78 [illegible]

CSKumkumian/lc/4/24/78

Senator HAWKINS. It states that you were contacted by this assistant associate and told of the concern of "over requesting" information and data by you and your chemists; that you had requested too much information. It further states that this Assistant Associate Director instructed you that in order to avoid any future problems, that all communication with NCI in regard to manufacturing and control for IND's, investigational new drugs, should be reviewed with him—him, being the Assistant Associate Director—before they are finalized.

Would you explain to us what you think was the purpose of this memo?

Dr. WOOD. I think the origin of this memorandum was two letters sent to NCI concerning two investigational drugs. I believe one was 2-deoxycoformycin, DCF; I do not recall offhand what the other investigational drug was. NCI, I believe, contacted the Director of the FDA Bureau of Drugs, and complained about the two letters that were sent, that they were over requesting; that is, asking too many questions on the chemistry and the manufacturing and controls information that we wanted to know about.

I would just like to point out that we did not stop any studies because of chemistry deficiencies. We simply pointed out areas we felt were deficient, trying to assist them in determining the information that they should get on this drug, such as the source of the drug, how it was manufactured, was it manufactured under good conditions, is the drug stable. These are important questions that assure that the drug is pure, reasonably pure, and certainly to the public's benefit.

Senator KENNEDY. Have you ever been accused of over requesting from private drug firms?

Dr. WOOD. I think this is a chronic problem, the complaint from industry—not specifically, for myself, but for the FDA, in general. Concerning investigational drugs, however, I have not, to my knowledge, been accused of "over requesting" by private drug firms. In fact, they have appreciated our comments because such guidance helps them later in the preparation of new drug applications.

Senator HAWKINS. Have there been any occasions when your requests for information from the NCI were changed or retracted by your superiors?

Dr. WOOD. It is my understanding our Division Director did write a memorandum indicating that he had contacted NCI and said that we were retracting the two letters concerned here.

Senator HAWKINS. Could you tell us what is the level of morale in your division at the present time?

Dr. WOOD. I cannot—well, I guess I could speak for the division. I will speak only for the chemists involved who, as I said, are a very small number. The number of chemists is about the same size it was 8 years ago when I first came to the FDA. Our staff has not increased a bit. The workload has increased to something like 66 new drug applications and resubmissions, over 230 investigational new drug applications, supplements, annual reports, and so forth, that have to be reviewed. I think this could be tolerable if we were not at the same time subjected to this pressure to compromise reviews and approve everything as fast as we can, without being sure about drug quality.

I think we are all very—we do not want to hold things up, but we want to be sure that the drugs are as pure as possible and the public will benefit from this.

Senator HAWKINS. Thank you, Dr. Wood.

Dr. Richman, you are the supervisory pharmacologist for the division?

Dr. RICHMAN. Yes, Senator.

Senator HAWKINS. And as I understand it, you have been with the FDA for 17 years; is that right?

Dr. RICHMAN. That is right.

Senator HAWKINS. Would you give us a brief description of the role of the pharmacologist in the review of NCI's application for use of investigational new drugs?

Dr. RICHMAN. It is the pharmacologist's job to review the pharmacology and toxicology information that is supplied by the sponsor, make an independent review, evaluate the data, make recommendations, point out deficiencies, if there are any. I believe the Washington Post quoted that it is a pharmacologist's job to define toxicity and a clinician's prerogative to ignore it.

Senator HAWKINS. It is obvious to me, from your work and your writings, that you are dedicated to the science of your profession. Is that perception correct?

Dr. RICHMAN. Thank you Senator, I try as best I can.

Senator HAWKINS. However, I understand that your dedication to provide the best expert advice so as to insure safety in the use of these drugs has made you controversial, not only at the NCI, but also with your superiors; is that correct?

Dr. RICHMAN. I am not sure that I am considered controversial; but——

Senator HAWKINS. Maybe effective.

Of primary concern to you, Dr. Richman, is NCI's new and abbreviated toxicology program for testing these drugs in mice and dogs before they are administered to humans; is it not?

Dr. RICHMAN. Yes, Senator.

Senator HAWKINS. Would it be accurate to say that professionally, you cannot understand why the NCI does not want to submit all of the data?

Dr. RICHMAN. That is true.

Senator HAWKINS. Especially the more refined data from animal tests, prior to testing these drugs in humans?

Dr. RICHMAN. Right.

Senator HAWKINS. How much of a delay do you estimate there would be if the NCI were to submit all of the animal test data before proceeding to clinical trials in human beings?

Dr. RICHMAN. Senator, I feel that if we waited for the histology to come in, it might add on an average 2 months to the submission. It is possible it might add as much as 4, but I think we also realistically can say that many times, if not most of the time, the histology will already be in the hands of the National Cancer Institute at the time they submit the jacket. So it would not really add any time extra, in that case and would allow FDA pharmacologists to make their own independent review in a timely fashion.

Senator HAWKINS. In one of your papers that we have relating to the review of the first of the NCI's drugs to be submitted under the new toxicology program, you wrote——and I will quote—"For the record, I wish to state that the protocol which I am being asked to implement is unsound and that I am severely distressed by the necessity of having to implement it." Do you still hold to that statement?

Dr. RICHMAN. I still hold to that statement, although it may be somewhat dramatic. I did want to go on record after being part of the debate as to the format the new guidelines for over 2 years. And I still stand by my reasons for my recommendations on the toxic guidelines as delineated in my review from which you just quoted.

Senator HAWKINS. And your estimation of the additional time you think it would take would probably be 2 to 4 months?

Dr. RICHMAN. Yes.

Senator HAWKINS. So we are not talking about 2 to 4 years.

[Dr. Richman's prepared statement follows:]

STATEMENT

BY

DAVID J. RICHMAN, PH.D.

U. S. FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE OF INVESTIGATIONS AND GENERAL OVERSIGHT

COMMITTEE ON LABOR AND HUMAN RESOURCES

U. S. SENATE

WASHINGTON, D.C.

November 3, 1981

Madam Chairman,

Members of the Committee,

While I welcome the Committee's Investigation of the National Cancer Institute's Drug Development Program and that program's regulation by the Food and Drug Administration, I appear today as a reluctant witness.

This hesitation to appear was based on several concerns including the knowledge that a scientist, at least this one, can think and articulate best when conferring in a quiet conference room, and least, in an unfamiliar forum in the glare of lights for TV cameras and the press of media coverage. What concerns me most is that a statement may be taken out of context or misconstrued by that media in such a way as to mislead those we all serve, the public, in a manner detrimental to them. As an example I would cite the Washington Post series of two weeks ago, "The War on Cancer," albeit well intentioned, which sensationalized problems of cancer chemotherapy in a manner which may have left many people with the wrong impression. Namely that all chemotherapeutic drugs are poisons and that none are effective. That type of journalism, unfortunately, can send potentially curable cancer patients into the hands of charlatans and quacks.

It should be noted that not all misdirected sensationalism is directed at the National Cancer Institute by its detractors. Over the years verbal and printed stones have been cast against the FDA's regulation of the drug development program. Often they have been hurled by unquestioning supporters of the Institute in the same sensationalistic manner that they feel is unfair when directed against the Institute. As a recent example I cite the October 23, 1981 issue of the Cancer Letter (exhibit 1) which deplores the lurid style of the "War on Cancer" series and decries the seemingly personal attack in it on Dr. DeVita - both observations not without some merit. The Cancer Letter then summarily ridicules an FDA medical officer and states as apparent fact that "All NCI has asked of FDA is that prospective anti-cancer drugs not be considered in the same category as new headache pills. Because so many cancer patients will die without some new therapy, NCI staff and cancer investigators feel it is not logical to demand as many safeguards as would be required for a new medicine designed to treat non-life threatening ailments." This statement seems to crop up with regularity. Often accompanying it is a specific point of fiction such as that the FDA requires two years of dosing animals with a new anticancer drug before allowing it to be given to the first cancer patient.

It might be of interest to learn just who leaks these monumental misconceptions and as to why they are published and perpetuated without being checked for factuality.

Since apparently I have been subpoenaed to testify on F.D.A.'s preclinical toxicity requirements for anticancer drugs, may I state, that in general, since the establishment of the IND procedures in 1963 the Agency has accepted the NCI toxicity guidelines. We have at times been even more flexible; e.g. we never required the use of the monkey as a second species when the NCI did so. Instead, we allowed a rodent species to be employed. Prior to 1973 the longest period of dosing animals before initial clinical trials was 30 days, and from 1973 until the latest NCI proposals, the longest period of actual dosing was 15 days.

As the Committee is aware, during the past two years the FDA and the NCI have debated with each other, and internally, as to proposed changes in the toxicity guidelines. These deliberations were both vital and appropriate. Distortions of FDA positions by certain elements of the press and by certain elements of the clinical oncology community are a disservice not only to the public and the F.D.A. but to those who foster perpetuation of this nonsense.

It should be made clear that the Washington Post was responsible enough to publish critical comments regarding their "War on Cancer" series and gave Dr. DeVita the opportunity to publish his rebuttal. The paper also had the common sense to publish an editorial regarding their own series on October 29, 1981 entitled "On the War On Cancer" which to me was a rational, thoughtful discussion regarding Phase I testing. If this editorial is not already part of the record I offer it to the Committee (exhibit 2).

During my fifteen years as supervisory pharmacologist of the FDA's Bureau of Drugs, Division of Oncology and Radiopharmaceutical Drug Products I have attempted to maintain a mutually beneficial liason with my colleagues at the NCI. I am an ardent supportor of the NCI, its programs, and its goals. I am proud, too, of the FDA, its tradition of service, its mission and - specifically for the purpose of todays hearing - what I consider its reasonable approach to regulation of cancer chemotherapeutics drugs.

It is not my feeling that the term "sister agency" consists of two dirty six letter words. I see no conflict of interest in my support of NCI programs and my duties as a regulator of the NCI drug development program for I believe it is our job at the Bureau of Drugs not only to keep unsafe and ineffective medications from harming the public - it is equally our responsibility to see the public is served by allowing effective drugs to reach them as quickly as feasible. In no area of medicine is this more important than in the field of cancer treatment. It does not mean we must slavishly yield to each of NCI's demands or pressures without a thoughtful examination of the merits of their proposals. Omnipotent wisdom from any source is not to be found on this earth.

My views regarding the proposed NCI revisions of their preclinical toxicity guidelines are a matter of record. This Committee has that record and I assume I am present to verify or clarify portions of it.

My deep concern that Phase I cancer patients, with little efficacy from their chemotherapy likely to be derived, have no needless suffering heaped upon them, is shared by all. How best to accomplish that goal without having lost the thread of hope for cure or palliation is a point of debate.

For the record I wish to state that my views regarding the toxicology guidelines modifications were given airing in considerable detail to my superiors within the FDA. This was especially true in the cases of the Director of the Bureau of Drugs and officials from the Commissioners Office. Indeed, they sought me out to have extremely frank and lengthy discussions. That my recommendations concerning toxicology guidelines, and what I believe in general represents the basic recommendations of most toxicologists, were not given support by most clinical oncologists was frustrating. It has occurred to me that it is possible that their reasoning might, of course, be more correct than ours.

It has occurred to me, too, that toxicologists would seldom challenge oncologists in their field of expertise so why do they overrule us in ours? A colleague of mine formerly with the NCI and now with the FDA is fond of noting that a toxicologist's job is to define the toxicity of drugs - that it is the clinician's prerogative to ignore it.

The scientific method is, thankfully, a difficult master to ignore in the course of time. It is noted, with some satisfaction, that the arm chair decisions of some regarding how toxicity studies were to be conducted, as proposed more than two years ago by NCI, have had to be modified substantially as problems were encounted in the real world of the laboratory. At this moment in time the protocol, evolving out of practical necessity, is moving ever closer to one proposed by Division pharmacologists last April in an attempt to resolve differences amicably, among all points of view of staff members at both the NCI and FDA.

At the heart of the issue of how much preclinical data to gather and how much time we should take to gather it prior to initiating a Phase I clinical trial is the benefit/risk assessment for the Phase I patient. Based on my 17 years experience at the FDA, my close contacts with the NCI, with clinical oncologists and toxicologists in the field, with other members of the American Association for Cancer Research, I see no reason to change my past recommendations regarding toxicology guidelines.

Most definitely I would rethink my position regarding preclinical requirements should hard data, rather than rhetoric, be forthcoming. If, indeed, 9.5% or any percentage near that amount of Phase I patients are "substantially benefiting" from chemotherapy - a statement attributed to the NCI Director at the October 27, 1981 subcommittee hearing chaired by Congressman Gore, then I would be here urging the most minimal animal studies prior to clinical trial.

Some ranking oncologists have pointed accusatory fingers at regulators and legislators and intoned the sad but vallu words - "If these cancer patients don't begin Phase I chemotherapy, 90% will be dead in a year." If they would instead offer evidence to show that less than 90% of those same patients would not be dead even had they entered those Phase I studies, I would be here urging the most minimal of animal testing. If they could offer evidence that the quality of life for those Phase I patients had also been improved rather than lessened, then indeed would I be here urging the most minimal of animal testing.

But, indeed, it may be assumed that if such positive data were available there would be no reason for you to have requested that I appear before you today.

The comments made in this statement and the testimony I will present may not represent the official position of the Food and Drug Administration.

Madam chairman, members of the committee, I will respond to questions that you or your committee might have.

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DRUG

POST STARTS SERIES WITH HORROR STORIES ON DRUG TESTING; DEVITA SAYS THEY ARE "SLANTED, DISTORTED"

The long developing *Washington Post* investigation of the National Cancer Program broke into print this week with the expected attack on clinical testing of experimental anticancer drugs. The consequences for clinical research could be devastating.

Two crack *Post* reporters, Ted Gup and Jonathan Neumann, have

(Continued to page 2)

In Brief

ADAMSON'S APPOINTMENT OFFICIAL AS DCCP DIRECTOR; NCI HOLDS CURRENT SPENDING TO 12 PERCENT LEVEL

RICHARD ADAMSON'S appointment as director of NCI's Div. of Cancer Cause & Prevention has now been made official. HHS Secretary Richard Schweiker approved the appointment this week. Adamson has been acting director of the division for more than a year. Adamson, 44, received a PhD in pharmacology from Iowa State Univ. in 1961 and joined NCI in 1963 as senior investigator in the Laboratory of Chemical Pharmacology. He became chief of that lab in 1973. During 1979-80 he was on leave from NCI to work as a senior policy analyst in the White House Office of Science & Technology Policy. . . . FY 1982 BUDGET picture for NCI and the rest of HHS remains bleak, with the Administration determined to extract a 12 percent reduction from its original proposal. NCI presently is operating at the continuing resolution level established by Congress in which spending is limited to the 1981 level of $989 million, prorated for the Oct. 1 to Nov. 20 period, when the resolution expires. Anticipating the possibility that the 12 percent cut will be imposed, NCI is holding its spending through Nov. 20 to the $902 million level, prorated—12 percent under the President's request of $1.026 billion. Congress is balking at the severe reductions in health and social programs, probably will settle on an appropriations bill with more money in it than the President wants, risking a veto. Congress is likely to sustain a veto, requiring more continuing resolutions, and the President still has the deferral and rescision options. The House has completed action on the bill, which would give NCI $1.030 billion. The Senate HHS Appropriations Subcommittee marked up its bill, with NCI at $1.034 billion, but the full committee has yet to act, and no date has been scheduled for it to do so. The pinch on NCI will not be felt until early 1982 when grant funding demands require more outlays. . . . MEANWHILE, NCI is bringing its advisors into the process of determining where the cuts will be made, if cuts there must be. Members of the National Cancer Advisory Board will receive lists of the Institute's programs and will be asked to rank them by priority. The four Boards of Scientific Counselors will receive similar lists of programs in their respective divisions.

NIH Says Its Probe Found Charges Of Double Payment "Basically Correct" . . . Page 5

NCAB Subcommittee OKs Concept Of Five Recompetitions . . . Page 6

RFPs Available . . . Page 7

Contract Awards . . . Page 8

EXHIBIT 1

WASHINGTON POST SERIES DWELLS ON DRUG DEATHS, ADVERSE REACTIONS

(Continued from page 1)

spent nearly a year investigating the Cancer Program. They told *The Cancer Letter* last November that they were taking on the project with "open minds, no preconceived ideas on the direction the investigation will take. We'll let the chips fall where they may."

The chips fell this week in the form of a series of horror stories in which Gup and Neumann claimed to have documented 620 instances where experimental drugs were implicated in the deaths of cancer patients. They selected some of the more gruesome and heart rending to describe in detail.

The four part series on testing of experimental drugs was scheduled to end Oct. 21. The *Post* said that in coming months, other areas of what it called the "War on Cancer" will be examined, including "the psychology of cancer doctors and patients, the causes of cancer and possible methods of prevention, basic scientific research in cell biology and genetics, and the politics of cancer."

The *Post* in its Oct. 19 issue used a rebuttal by NCI Director Vincent DeVita to the opening article. DeVita submitted another response the following day to the second article, which was not used, and planned to follow with others.

The series opened with a set of statements by the reporters describing conditions which, while it may have been news to the two reporters, certainly was not to clinical investigators:

"While all anticancer drugs can cause side effects among some of those who take them, the experimental drugs—in addition to leading to hundreds of deaths—have elicited a nightmarish list of serious adverse reactions, including kidney failure, liver failure, heart failure, respiratory distress, destruction of bone marrow so the body can no longer make blood, brain damage, seizure, coma, and visual hallucinations.

"So little is known about many of these chemicals that doctors have found these ironic results: In some cases the experimental drug actually stimulated tumor growth rather than stopped the cancer; and in other tests, doctors and researchers found that the experimental drugs themselves caused cancer.

"In many cases, the experimental drugs have been given to patients even years after studies failed to show that they were of use in the fight against cancer. The first phase of the experimental drug program, in fact, is primarily designed not to combat cancer but to find out how toxic the drugs are."

The first article went on to claim that evidence of mismanagement of patient records at leading hospitals and cancer centers, miscalculation of doses with fatal results, administration of drugs not approved by the FDA for human use and not authorized by NCI.

"The litany of death and suffering from experimental drugs has become an accepted part of life at some hospitals around the nation," the article said.

The opening article included a couple of quotes by Robert S.K. Young, the former FDA oncology group leader who appears to have dedicated his career to opposing anticancer drug development and testing. About five years ago, investigators found one IND application after another blocked by Young, sometimes for nitpicking technical reasons, sometimes for no apparent reason at all. He fiercely opposed the new toxicology protocol which substantially reduced the cost and time of getting drugs into the clinic. When the protocol was approved by FDA's own Oncologic Drugs Advisory Committee (after being approved by the Board of Scientific Counselors of NCI's Div. of Cancer Treatment), and then was approved by the director of FDA's Bureau of Drugs, Young resigned as group leader and carried on his fight. The FDA commissioner recently threw out Young's citizen's petition against the new protocol.

Nevertheless, Gup and Neumann selected a man whose views had been disavowed by the scientific advisors to both NCI and FDA and by his own superiors to feature in their lead article. Young did provide them with some grabby statements:

—"Sometimes there is little regard for people's lives. In Boston a hospital tested a new NCI drug on children. Their kidneys were lost within days. This was no big deal, because NCI new drugs are routinely given out with literally no safeguards for people who will receive them."

—"There are so many analogies between the 'War on Cancer' and the war in Vietnam. It's scary. You've got the generals, the NCI. And you have this attitude among the generals: 'We have to burn the village to save it.' "

That set the tone for the series. There followed case histories, with patients, their physicians, and sometimes family members and nurses, all being named. Most ended with the patients' deaths, usually caused by the drugs, always after enduring agonies from drug effects.

The articles have dwelled on repeated use of the same drugs in phase 1 studies despite the severe side effects and despite lack of beneficial effects for the patients.

The *Post* so far has used two positive sidebars by Gup and Neumann. One dealt with the development of cisplatinum as a successful anticancer agent. The article noted that the drug was almost abandoned because of severe kidney toxicity but that a method was developed to overcome that problem and cisplatinum is now one of the most successful drugs against some forms of cancer.

The other positive article reported on a 13 year old Maryland girl treated at Johns Hopkins Oncology Center for neuroblastoma. After surgery and chemotherapy failed to keep her in remission, her physicians—Brigid Leventhal, Herbert Kaiser, and David Hall—proposed using high doses of adriamycin and cytoxan with autologous bone marrow transplant. That worked, and the girl has been free of disease for two years.

In several of the case histories reported in the first article, Gup and Neumann cited drugs as failures which appeared on the high priority list of drugs going through NCI's Drug Development Program in 1979. Each time, they pointed out this was one of the "high priority drugs listed by DeVita in 1979."

The Washington Post-Los Angeles Times News Service distributes articles from the two newspapers to other subscriber newspapers around the country. The Gup-Neumann articles have appeared in other papers, although not (as of *The Cancer Letter's* press time) in the *Los Angeles Times.* DeVita's first response apparently has not appeared in many, if any, of the papers. The *Post* series also is being distributed, summarized, by the Associated Press.

As a service to Cancer Program advocates who may wish to combat the negative aspects of the *Post* series, *The Cancer Letter* will publish each of DeVita's responses. Following is the first, which may be clipped and reproduced without further authorization:

> The article by Ted Gup and Jonathan Neumann in the Post Oct. 18 presented a tragic lack of understanding of cancer treatment and the national program to develop drugs that are effective in treating cancer.
>
> It bears repeating that cancer patients—and the doctors treating them—have as their first goal the successful treatment of the disease. In this context, many patients feel that it is worthwhile putting up with side effects of treatment knowing that the treatment may prolong their lives or provide a cure. All of us who work on the cancer problem wish there were no side effects related to treatment, and much of our work now is to develop treatments that are effective without causing side effects.
>
> It also bears repeating that, contrary to the impression left by the article, much progress has been made in treating cancer. Of the 785,000 patients diagnosed with serious cancers in 1980, 356,000—45 percent—are potentially curable. This includes 220,000 patients curable with the oldest treatment, surgery; 90,000 patients curable by surgery combined with radiation therapy, a treatment that has come into its own only since 1947; and about 46,000 curable as the result of adding chemotherapy, the newest form of cancer treatment.
>
> The article did not mention that cancer mortality rates are falling in the age group under 45 years old. It did not mention that survival rates have increased significantly for seven of the 10 major forms of cancer in whites and six of the 10 in blacks. These major gains are among cancers of the breast, colon, rectum, bladder and prostate, to mention some. In addition, survival gains for cancers striking young Americans are even more substantial. These cancers include childhood leukemia, Hodgkin's disease, testicular cancer and others. Unfortunately, not all patients with any type of cancer are cured so it is essential to continue research to develop better treatments.
>
> Several points need to be made about the distortions in the article:
>
> One, Gup and Neumann totally missed the concept that anticancer drugs are meant to be used in combination with other forms of treatment, such as surgery and radiation, and that they are expected to be most effective in treating early cancers. For ethical reasons, all drugs are first tested against advanced cancers afflicting patients for whom no other hope exists. Even a few responses against advanced cancers can mean major effect against early cancers, particularly when the drugs are used in conjunction with surgery and radiation therapy.
>
> Two, the writers state that they have documented 620 cases where experimental drugs were implicated in the deaths of cancer patients. Any death associated with treatment causes anguish to the family of the patient, to those who were providing the care, and to those of us who are working to help all cancer patients. The fact remains, however, that such cases are unusual. Gup and Neumann did not mention that hundreds of thousands of patients have participated in our research programs to develop anticancer drugs. Remember also that 46,000 patients are cured every year because of anticancer drugs. The contrast between lives saved and risks taken is striking.
>
> Three, the article did not make clear that most drugs side effects are temporary, predictable, and manageable with standard techniques. Different patients experience different effects, and some experience no side effects at all. As I noted above, much research now is devoted to reducing side effects and developing new drugs with few side effects.
>
> Four, the article implied that studies of particular anticancer agents are carried on long after the compounds have been shown to be toxic and after they were shown to have little effect in treating particular types of cancer. Again, Gup and Neumann missed or are ignoring the fact that specific anticancer drugs often work only against a specific type of tumor. When a drug is tested in patients it is done at many different dose levels, schedules of administration, and against a variety of different cancers. If a drug proves to be ineffective against one or more types of cancer, it does not mean it will not be effective against other cancers. Cisplatinum, a drug whose success the writers described, is not effective against all cancers. In other words, early discouraging results do not mean an experimental drug will not be effective against another tumor yet to be tested.
>
> Five, Gup and Neumann repeatedly referred to my 1979 list of high priority drugs. But they twisted the meaning of that list, implying that I was predicting these drugs would have great beneficial effect in patients. My 1979 list was of drugs that had performed well in animal tests, and therefore had high priority for human testing. There were no predictions that any of those compounds would become miracle drugs for treating people.
>
> Six, in discussing particular anticancer drugs, such as MeCCNU, Gup and Neumann point to side effects of renal failure and acute leukemia. These are delayed side effects that develop slowly and are difficult to detect and difficult to predict with any animal testing. The kidney problems with MeCCNU, for example, showed up as an acute, or immediate, effect in the animals, but did not show up as an immediate problem among patients who received the experimental drug. The first case in humans was not detected until more than a year after the patient had stopped receiving the drug and after several years of use with patients. Under such circumstances, the development of kidney damage in a cancer patient with a long history of the disease and many treatments can be difficult to link with any one drug when the observation is made for the first time.
>
> Seven, Gup and Neumann imply and quote a cancer expert as saying that Phase I studies provide patients no potential for cure. This is clearly a distortion of what occurs. Phase I studies do sometimes result in significant responses, and the drug vincristine provides a striking example. Potential for beneficial effect exists and is an important part of the ethical

base for conducting such studies.

Eight, Gup and Neumann consistently make the point that only six drugs are effective in treating cancer. That, too, is just plain wrong. There are more than 40.

In summary, it is unfortunate that the Post, particularly now that Washington is a one-newspaper city, has chosen to present such a slanted and distorted view of cancer research. Gup and Neumann should keep in mind one important point: cancer is lethal if left untreated. The possibility of treatment side effects and the small but real chance od drug-related death has to be balanced against the nearly 100 percent chance of death if experimental therapy is not attempted for the advanced cancer patients who participate in our studies. All cancer patients experience anxieties and doubts at one time or another during treatment. It would be tragic if cancer patients who read this article, and those that will follow, turn away from their treatment.

Solomon Garb has seen the cancer problem from both sides. A clinical pharmacologist who dedicated his career to finding better treatments for cancer, he has been a cancer patient himself now for almost a year. He has been battling stomach cancer, first with extensive surgery, and then with chemotherapy. So far, there has been no recurrence, but he has paid the price with severe side effects from the drugs. He almost died from reaction to treatment last April.

"I don't mind," Garb said Monday. "I'm just glad to be alive. It's been tough, but I'll take treatment over the alternative any time."

Five year survival with stomach cancer is 10-15 percent, with most recurrences coming within the first 18 months. Garb figures he is within sight of beating it.

Garb was dismayed by the *Post* articles. He sees it not only as a threat to progress by discouraging patients from participating in clinical trials, but also as a threat to the entire National Cancer Program. As chairman of the Citizens Committee for the Conquest of Cancer, Garb was a leader in the movement which led to the National Cancer Act of 1971. Much of his time in the years since has been spent fighting to keep the Act intact, and fighting for the money to properly implement it.

Garb had a suggestion for Cancer Program advocates for action they might take if their local newspapers use the *Post* series or any part of it: "Go see the editor and take Vince DeVita's statement with you." Local AP bureau chiefs also might be interested in DeVita's response, he said.

Garb said he agreed with one aspect of the series. "A lot of us have argued for years against phase 1 studies. We don't think they are necessary. They can be combined with phase 2. The argument there is not with us (clinical investigators) or NCI, but with FDA."

The opening article included statements from DeVita and others. His was the only one which could be considered positive.

"I believe sincerely that patients want those therapies, they want to go into phase 1 studies," DeVita was quoted as saying. "Patients do not want to go out of this world without trying in the majority of cases. You stop putting cancer drugs out there and there will be an avalanche of people clamoring for drugs."

Michael Hensley, who the *Post* said was an FDA investigator, reportedly said, "Cancer chemotherapy is off limits for FDA investigators. The rule book is thrown out when it comes to cancer chemotherapy. I don't know if it's written in as many words, but there's absolutely no question about it. Ask anyone around here. I have been told many times that NCI was off limits."

All NCI has asked of FDA is that prospective anticancer drugs not be considered in the same category as new headache pills. Because so many cancer patients will die without some new therapy, NCI staff and cancer investigators feel it is not logical to demand as many safeguards as would be required for a new medicine designed to treat non-life threatening ailments. If Hensley was told NCI is "off limits," (whatever that may mean), it was because his superiors were overreacting to NCI opposition to the type of nitpicking they endured from Young.

Linus Pauling was quoted as saying, "Why make the patient miserable for his last few days. I don't think the terminal cancer patients should be used as guinea pigs. You have to carry out human experiments to make progress, but you must be careful that you don't sacrifice human beings."

Charles Moertel, director of the Mayo Comprehensive Cancer Center, was quoted as saying, "The state of the art, generally, it's awfully rudimentary. We have hit on some areas more or less by luck. We have accomplished a lot but it's been like swatting flies with a sledge hammer. It's been rather blind. I suppose as far as end products are concerned it's been a bust, but then so is the overall treatment of cancer."

Vincent Bono, who until earlier this year was chief of the Investigational Drug Branch in NCI's Div. of Cancer Treatment, was quoted as saying, "In phase 1 or phase 2, human beings are actually being used as guinea pigs. Phase 1 is like donating your body to science while you are still alive."

The *Post* series gives more ammunition for Sen. Paula Hawkins (R.-Fla.) to shoot at DeVita in the hearing scheduled for her Labor & Human Resources Subcommittee on Investigations & Oversight Nov. 3. Hawkins took the floor of the Senate this week to quote from the articles and to say she has found "dangerous deficiencies" in NCI's Drug Development Program.

The hearing will start at 9 a.m. in the Dirksen Senate Office Building, Room 4232.

On 'The War On Cancer'

IN ALL OF clinical medicine, few situations pose as many heart-rending choices for patient, family and doctor as the terminal stages of cancer. It is the time when everything known to be effective against this still utterly mysterious disease has failed, when a doctor must either do nothing or venture into the high-risk world of experimental treatments, and when a patient often must choose between loss of hope or another round of expectation followed by crushing disappointment.

Aspects of this world were explored in The Post's series, "The War On Cancer," last week. The series took on a valid and difficult subject and performed a service by launching a broad public discussion on an issue of great concern. It dealt with early clinical testing—so-called Phase I trials—of potential anti-cancer drugs. The series criticized these tests, which are run by the National Cancer Institute, for being designed primarily to determine drug toxicity rather than efficacy, for inflicting excessively toxic side effects on patients, including 620 cases of drug-related death, for errors in calculating proper dosage and sloppy record-keeping, and for continued testing of drugs "even years after studies failed to show that they were of use." It described drugs "derived from a list of highly toxic industrial chemicals including pesticides, herbicides and dyes" that have created a "litany of death and suffering" in "human experiments" where patients become "laboratory subjects." Most seriously, the series questioned whether the tests violate the physician's guiding tenet "first do no harm."

The pain endured by patients who agree to participate in experimental drug testing is often great, but must always be understood in the light of three fundamental facts. First, such patients are terminal; their life expectancies are generally a few weeks or months, and every known therapy has been exhausted. Second, because the causes of cancer are still unknown, doctors and drug designers must rely on the simple observation that cancer cells grow and divide where normal cells would not. This means that agents that prevent cells from growing or dividing will kill cancer cells faster than they kill normal ones. Thus chemotherapy, like other cancer treatments is, *by definition*, a toxic process. Finally, cancer, despite its name, is not one disease, but dozens of different ones.

Many of the otherwise inexplicable aspects of Phase I testing described in The Post's series are understandable in this light. Drugs must be tested on a variety of tumors before being discarded as ineffective. Therefore a drug may still be being tested years after early tests have shown no benefit. As with any type of new drug, doctors must find the right dose level and schedule of administration by a process of informed trial and error; there is no other way. In these early stages of testing, even the best drugs will be more toxic and less effective than later on when used in the optimal dose, in combination with other drugs, and against earlier, more susceptible stages of the disease.

Though mistakes have surely been made in record-keeping and reporting of results, the record for experimental chemotherapy does not appear to be any better or worse than in other areas of medicine. Most important, an experimental drug's low chance of success and high risk of causing toxic side effects must be balanced against the patient's high risk of death. As some of today's letters indicate, many patients are also performing the hardest balancing act of all: weighing their own low chance of benefit against their contribution to those who come after.

There are serious issues relating to experimental chemotherapy. The NCI's large clinical testing programs may be shortchanging research programs, in pathology, toxicology and pharmacology, that could make cancer treatment more effective and less painful. Some doctors may be losing sight of the individual patient's welfare in their zeal for research. But finding the middle ground between the quality of life for a dying patient and the possibility of finding a cure for others is not easy. For some patients, the best thing is do something, even something painful. For others it will be different. Ultimately these choices depend on the wisdom and humanity of individual doctors.

WASHINGTON POST,
29 OCTOBER 81

EXHIBIT 2

PHARMACOLOGY AND TOXICOLOGY REVIEW OF IND 18,905

SEP 2 1981

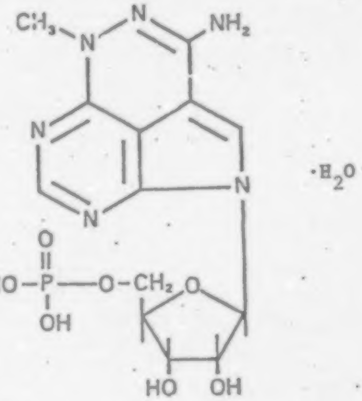
Original Summary

Date Review Completed: June 23, 1981

SPONSOR: Division of Cancer Treatment
National Cancer Institute
Bethesda, Maryland 20205

SUBMISSION: Original IND dated June 23, 1981, Received in HFD-150 on June 24, 1981 and assigned to reviewer on July 2, 1981.

DRUG: Tricyclic Nucleoside 5'-Phosphate
NSC 280594
Tricycloside phosphate
Triciribine phosphate
TCN-5'-PO_4 or
TCN-P



1,4,5,6,8-Pentaazaacenaphthylene-3-amine, 1,5-dihydro-5-methyl-1-(5-O-phospho-β-D-ribofuranosyl)-, monohydrate

The drug is for injection (50 mg/vial)

CATEGORY: Antineoplastic

PROPOSED CLINICAL STUDIES:

This study will determine the maximum tolerated dose of the drug when administered by a 5 day i.v. schedule. The starting dose will be 30 mg/m^2 I.V. in 1000 ml normal saline by continuous infusion over 24 hours daily X 5 days. The first two escalation steps will be 60 mg/m^2/day X 5 and 100 mg/m^2/day X 5.

RELATED DRUGS/IND/NDAs:

IND 18,308 (Sangivamycin NSC 65,346)

PRECLINICAL STUDIES:

Tricyclic Nucleoside 5'-phosphate is the first drug to undergo preclinical toxicology testing using the token toxicology program, and as such is short on data. Included in this IND are the following:

a) Vasotoxicity Study in the Rabbit Ear Vein
b) I.V. Toxicity in CDF$_1$ Mice and Beagle Dogs
c) Antitumor Activity

PHARMACOLOGY:

Antitumor Activity:

Studies were conducted at the following laboratories:
a) Aurthur D. Little, Inc., Cambridge, MA
b) IIT Research Institute, Chicago, IL
c) Mason Research Institute, Worcester, MA

TCN-P was active against implanted L1210 leukemia in CDF$_1$ mice by both the i.p. and i.v. route of administration. No activity was observed with the p.o. route. The effect of the drug was greatest following daily administration for 9 days which resulted in an 85% ILS. No animals survived to thirty days on any schedule. I.V. administration was more toxic than I.P.. and a 50% ILS was achieved with 24-80 mg/kg/inj X 5 days with no deaths. However, the high doses resulted in weight changes (test-control) from - 1.8 to -5.7g. The drug was also active against the i.p. implanted P388 lymphocytic leukemia - no data was presented for this system.

Antitumor effects were also shown against the murine s.c. implanted CD8F$_1$ solid mammary carcinoma - 100 mg/kg/inj. X 5 weeks i.p. produced a 93% inhibition of tumor growth, with 20% of the animals showing no palpable tumor on day 30. The weight loss was not over - 1% for this dosage group. Activity of TCN-P was shown against the MX-1 mammary tumor xenograft implanted beneath the renal capsule of athymic mice.

ACUTE TOXICITY:

MOUSE:

Compound: NSC-280594 Lot #MS-01-188-2 and MS-01-196.
Formulation: 40.0 mg/ml in sterile water, NaOH(0.5N) was added to effect soln., then 0.1N HCl was used to adjust to pH 7.2. Further dilutions were made with 0.9% saline. The volume for administration was 25.0 ml/kg.

Route: I.V. into lateral tail vein.
Species: CDF$_1$ mice
Study Site: Raltech Scientific Service, Madison, Wisconsin.

	Male mg/m2	Female mg/m2	Combined Sexes mg/m2
LD$_{10}$	700	668	675
LD$_{50}$	863	770	819
LD$_{90}$	1064	887	994

Animals were observed for 29 days, with day 1 being the day of treatment. The majority of deaths occurred between day 3-5 in males and days 2-4 in females. No deaths occurred after day 15. Toxic signs included hypoactivity, ataxia, ruffled fur, decreased limb tone, diarrhea, hypothermia, bradypnea, impaired use of hind limbs, tremors, prostration, and black material adhering to the urogenital region. All treated groups showed slight to moderate decrease in mean body weights. Females recovered faster from the toxic signs than the males.

Five Daily Dose Lethality Study

	Male mg/m2	Female mg/m2	Combined Sexes mg/m2
LD_{10}	267	340	308
LD_{50}	418	429	423
LD_{90}	655	541	581

In addition to the above toxic signs, urine stained abdomen, impaired righting reflex, tremors, hair loss around eyes, ocular discharge, and prostration were recorded for this five daily dose study.

DOG - Single Dose Study:

Compound: NSC-280594 Lot #MS-01-188-2
Formulation: Same as for the mouse
Route: i.v. in left cephalic vein at 10 ml/min. Dogs receiving 3 ml or less were given an i.v. push.
Species: Beagle dogs 8-12 months of age at the start.
Number: 2/sex/dose
Dose: 68, 338, 676 mg/m^2 (3.4, 16.9, 33.8 mg/kg)
Study Site: Raltech Scientific Service, Madison, Wisconsin

Observed Effects: High dose animals showed emesis, white-foamy or food like emesis, hypoactivity, weakness, yellow sclera, orange urine was excreted almost daily throughout the study, black-red stools and diarrhea, fasciculations in all four limbs of one dog, blood red upper gingiva, yellow discharge from eye, red vulva in one female and bloody stools.

The mid dose dogs had emesis, diarrhea, food-like emesis, orange-red mucus, and dark stools. These dogs did not excrete orange urine.

Low dose animals produced bloody, grey, or soft stools on occasion. No orange urine was excreted by this group.

Mortality: One high dose male died on day 5, the other died on day 16. All other drug dosed animals were sacrificed in good condition on day 8 or day 58.

Body Weight/Food Consumption/Water Consumption:

One male became emaciated and lost 31% of its weight by the time of death (day 16). The other three high dose dogs showed a 7 to 18% decrease in body weight. By day 58 weight loss was regained in one dog. Mid dose animals had low food consumption on several days. Weight loss was large (7-23%) in three dogs with only partial recovery in one animal. The low dose group showed only minor changes in these parameters.

Hematology/Coagulation/Bone Marrow:

Hct and Hb values decreased in 3/4 dogs on the high dose drug and in 1/4 dogs in the mid group. RBCs values were extremely low, as were the Hct and Hb levels in the high dose animal which died on day 15. These parameters were normal in the other high dose male which died on day 5. The reticulocyte value increased in one high dose female on several occasions. WBCs were increased in 3/4 high dose, 1/4 mid dose, and in 1/4 low dose dogs; these values returned to normal by day 57. Mature neutrophils were elevated in the high dose group and were often accompanied by a decrease in the lymphocyte percent. The eosinophils were increased on several occasions in 1/4 high, 2/4 mid, and 1/4 low dose animals. Platelet values were decreased in 3/4 high dose dogs, and at termination all platelet values were normal or slightly above normal.

Prothrombin times were severely increased in 3/4 high dose animals on day 4 then returned to the normal range by day 8 and thereafter.

Blood Chemistry:

AP values were increased moderately to severely through the study in the high and mid dose dogs --- values 17 times higher than the baseline data were recorded.

SGOT values were increased 10-24 times above baseline values in the mid and high dose dogs on days 2 and 4. SGPT values were also elevated (52 times baseline) in the mid and high dose dogs on days 2, 4, and 8. Levels remained high in several dogs up to termination.

BUN values were mildly elevated above the baseline values in 1/4 low, 3/4 mid, and 2/4 high dose animals.

Total and direct bilirubin values were elevated (up 42 times) in 3/4 high dose animals on day 4 and in 2/4 animals on day 8. The mid dose group also had mild elevations in the direct and total bilirubin values on days 2 and 4.

Chloride values were moderately decreased in the two high dose males which died. Sodium values were also decreased. The serum potassium level was decreased somewhat in one of these dogs prior to death. Ca levels were mildly increased in one mid dose female on day 43 and decreased in 1/4 mid dose and 3/4 high dose dogs on several occasions.

DOG - Five Daily Dose Study:

Number: 2/sex/dose, 1/sex in the control
Dose: 0, 30, 154, 308 mg/m^2 (1.5, 7.7, 15.4 mg/kg)
Control Treatment: 0.38 ml 0.9% saline/kg/day, this volume is equivalent to that given to the high dose dogs.
Study Site: Raltech Scientific Service, Madison, Wisconsin

Observed Effects:

High Dose: green mucoid diarrhea, orange urine, hypoactivity, yellow sclera, bloody mucoid diarrhea, ptyalism, prostrate, food-like emesis, swollen nictitating membranes, green mucus, blood in urine, stiff limbs, and orange diarrhea.

Mid Dose: mucoid soft stools, greenish mucoid diarrhea, hypoactive, hind limbs stiff, black-tary stools, dehydration, emaciation, yellow sclera, pale mucous membranes, yellow gingiva, moribund condition.

Low Dose: green diarrhea, mucoid stools

Mortality:

High: One male and female died day 5, one male died day 6, one female died day 8.

Mid: Male and female sacrificed day 8, female sacrificed day 85, male sacrificed in moribund state on day 35.

Low: One male and female sacrificed day 8, one male and female sacrificed day 65.

Body Weight/Food Consumption/Water Consumption:

All animals in the high dose group had a reduction in food and water consumption, and all showed a 7-10% weight loss. Two mid dose animals lost 12% in body weight by day 8 when sacrificed. One female lost 15% of its original body weight by day 15; the final weight at day 65 was 11% below the initial weight. The moribund male which was sacrificed on day 35 lost 50% of the initial body weight.

Hematology/Coagulation/Bone Marrow:

Low dose: slight elevation in WBCs in one male and platelets elevated in two females on several days.

Mid dose: The moribund male showed a decrease in Hct, Hb, RBCs, platelets, and lymphocytes, and an increase in WBCs and neutrophils. The WBCs were increased on day 29 in one female; the reticulocytes were also elevated in this animal.

High dose: Platelets were decreased to the low end of the baseline value by day 4 in all four dogs.

The prothrombin time of one high dose dog was moderately increased,and one mid-dose dog which was sacrificed on day 8 showed an increase in prothrombin time.

Blood Chemistry:

Low dose: BUN increased above baseline data on day 2 in one male.

Mid dose: The moribund male showed markedly elevated BUN, AP, SGOT, SGPT and bilirubin values on day 35. AP, SGOT, SGPT, PT, and bilirubin (total and direct) were severely elevated above the baseline values on day 8 in one female; its BUN value was only slightly elevated.

High dose: All animals showed an increase in AP values on days 2, 4, and 8. SGOT increased from 2.5 -62 times the baseline value. Likewise SGPT values increased 12-69 times over the baseline value from day 2 through day 8. PT values increased mildly to severely in 3/4 dogs. Bilirubin (total and direct) values were elevated 2-10 times above the baseline value in 3/4 dogs. Cl was decreased 10% in 3/4 animals, and one dog developed a decrease in Ca, Mg, and total protein.

SPECIAL STUDIES:

Vasotoxicity of NSC 280594 in the NZW Rabbit Ear Vein

The drug was elevated as the clinical formulation at doses of 2.5, 5, 10, 20, and 40 mg/kg/day (27.5, 55, 110, 220, and 440 mg/m^2/day) X 5 in 2 or 4/sex/group. The bulk formulation was tested at 40, 60, and 120 mg/kg/day (440, 660, and 1320 mg/m^2/day) X 5 in 1/sex/group. Both animals at the 120 mg/kg/day dose died on day 4 and the female in the 60 mg/kg/day group died on day 5 prior to necropsy. No other drug treated rabbit died. Histologic evaluation was done only on each ear and was evaluated for vasotoxicity.

There was no significant vasotoxicity caused by NSC 280594. The highest severity rating (0 through 5) was +2 which was observed in one 5 mg/kg, two 10 mg/kg, and one 20 mg/kg rabbit. Both 40 mg/kg rabbits were rated at +1.

SUMMARY AND EVALUATION:

Tricyclic nucleoside 5'-phosphate is the first drug to be tested under the new toxicology guidelines. This drug was synthesized in 1977 and shows only weak to modest activity when tested against the i.p. implanted L1210, the human MX1 mammary xenograft implanted beneath the renal capsule, and in P388 lymphocytic leukemia, or the CD8F1 mammary carcinoma. No activity was observed when tested against the Lewis lung carcinoma, the B16 melanoma, the colon 38, CS-1, on the LX-1 tumors. The drug was more effective with a daily i.v. schedule than with a single i.v. dose.

Toxicologic evaluation was performed by Raltech Scientific Services in CDF$_1$ mice and in Beagle dogs. The mouse X 1 LD$_{10}$ = 225 mg/kg (675 mg/m^2). The mouse X 5 LD$_{10}$ was 103 mg/kg (308 mg/m^2). Most deaths occurred between days 3 and 10 in the X 5 study, with no deaths occurring after day 22. Toxic signs observed in the mouse (both X1 and X5 study) included hypoactivity, ataxia, ruffled fur, decreased limb tone, diarrhea, hypothermia, bradypnea, impaired use of hind limbs, tremors, prostration, and weight loss. Females recovered slightly faster than males.

In the single dose dog study, animals were dosed at 3.4, 16.9, and 33.8 mg/kg (68, 338, 676 mg/m^2) which is equivalent to 1/10 LD$_{10}$, 1/2 LD$_{10}$, or LD$_{10}$ in the mouse. The X 5 dog study was done at 1.5, 7.7, and 15.4 mg/kg (30, 154, 308 mg/m^2). Toxic signs were dose related and involved GI, hepatic, and neurologic damage. The major hematologic abnormalities include anemia which was seen in the mid and high X 1 groups and in the mid dose X 5 group. Thrombocytopenia was seen in both the X 1 and X 5 schedule and was usually minor. WBCs were increased as were neutrophils. Fluctuation in reticulocytes occurred in both schedules. Eosinophils increased in both schedules. Prothrombin times were markedly increased in several animals in the high dose X 1 schedule. Liver enzymes (AP, SGOT, and SGPT) were drastically elevated in both schedules. These values were as high as this reviewer has ever seen. Bilirubin, both total and direct, were elevated. Cl, Ca, Mg, Ca, and total protein values varied in a few animals.

In conclusion, the drug is considerably more toxic in the dog than in the mouse, based on body surface area. In both species toxicity was greater in the male than in the female.

We agree with the statements (p. 159) by Batteile that "Probably all of the clinical chemistry parameters measured were reversible, but since many of the changes occurred prior to the death of the dogs, it is not possible to declare creatinine, Mg, and total and direct bilirubin changes to be reversible. The possibility of liver damage and perhaps kidney or cardiac damage is supported by the observed changes in clinical chemistry parameters." We also understand that the guidelines specify (see Dr. Crout's Memo of July 9, 1981, p. 5) that in the event of possible irreversible injury in the animal studies, additional toxicology studies directed toward the specific problem would need to be done before evaluation of the drug could begin in humans. These new guidelines also state that the initial IND submission would include gross pathology in the dog. This information was not submitted and therefore this IND is incomplete.

We also note that the proposed clinical trials to be conducted at M.D. Anderson will start at 30 mg/m^2/day X 5 days, with a continuous 24 hour infusion, and is said to represent 1/10 of the LD$_{10}$ in mice (p. 306). The animal data shows that the drug was considerably more toxic in the dog; the mouse LD$_{10}$ in the dog killed 4/4 of the dogs (see pages 157, 159, 178, 188 back, 195, 196 back, and 199). The starting dose in the clinic should have been based on 1/3 the TDL in the dog. Assuming the TDL to be 30 mg/m^2 (no discussion was given defining the TDL), then the starting dose should be 10 mg/m^2. It should also be mentioned that no preclinical continuous 24 hour infusion study was done. The sponsor has apparently not followed the guidelines.

It was interesting to note that Battelle had insufficient time to review the reports and summaries from Raltech for QA compliance. It was also noted that the QAW and GLP statements which were submitted did not cover the vasotoxicity studies conducted by Battelle Columbus Labs. It is the responsibility of the sponsor to see that nonclinical laboratory studies are conducted in compliance with GLPs.

The sponsor has not identified or given the qualifications of the individuals who evaluated the results of the preclinical studies and concluded that this drug is reasonably safe to initiate clinical investigations (see 312.1(a)(2)6(a) of 21 CFR).

Since the last dog in the dog X 5 study was necropsied on March 17, 1981 (a QA inspection was also done on this date), it would seem reasonable to assume that the histopathology has been done and is available for evaluation - the gross pathology should have been included with this submission.

Inasmuch as this is the first submission from NCI under the new proposed guidelines, it is to be expected that the sponsor would overlook several items of importance. It is hoped that further experience with these guidelines will produce more complete submissions from NCI such as we have come to expect from the pharmaceutical companies.

In summary, I do not find the data sufficiently convincing to state that tricyclic nucleoside 5'-phosphate is reasonably safe to introduce into clinical studies. This IND has several serious errors.

RECOMMENDATIONS:

The following recommendations are to be transmitted to the sponsor. Several of these requests have already been discussed with Dr. Lowe (NCI) in the phone conversation of July 17, 1981.

1. The Battelle report states the "The possibility of liver damage and perhaps kidney or cardiac damage is supported by the observed changes in clinical chemistry parameters."

Further, the guidelines state that in the event of possible irreversible injury in the animal studies, additional toxicology studies directed toward the specific problem would need to be done before evaluation of the drug could begin in humans. Therefore, it is requested that additional preclinical studies be done prior to the clinical testing, which will resolve the question of liver, kidney, and cardiac damage.

2. The starting clinical dose should have been based on 1/3 the TDL in the dog, since this is the most sensitive species. Please explain how you arrived at 30 mg/m^2 to be the TDL in the dog.

3. Quality Assurance Unit and GLP statements are requested for the vasotoxicity studies conducted by Battelle Columbus Labs.

4. The sponsor should identify and give the qualifications of the individuals who evaluated the results of the preclinical studies and concluded that NSC 280594 is reasonably safe to initiate clinical investigations (see 312.1(a)(2)6(a) of 21 CFR).

5. If the gross and histopathology have been done, please submit these data. The guidelines state that the gross pathology are to accompany the IND submission.

AWCoulter
A. W. Coulter, Ph.D.

cc:
Orig. IND 18,905
HFD-150
HFD-180
HFD-150/AWCoulter:7/23/81
HFD-150/CSO/LRipper
F/T:jb:8/11/81:Wang 5007A(12)

See Dr. Richmans addendum.

IND 18,905

SUPERVISORY PHARMACOLOGIST'S REVIEW SEP 2 1981

Supervisory Pharmacologist's Addendum to the Original Review:

It is painfully obvious that although more than two years have elapsed since the subcommittee of the FDA Oncology Advisory Committee issued its recommendations as to a format for preclinical studies to be conducted prior to phase I clinical trials of oncolytic agents, the National Cancer Institute has not been able to finalize a working protocol and submit an IND application that follows it in all particulars. This is not a major surprise since the original recommendations were essentially those of clinical oncologists, while the three nationally reknowned toxicologists acting as consultants to the subcommittee (Drs. Mihich of Roswell Park, Phillips of Memorial Sloan Kettering and Dixon of the National Institute of Environmental Health Sciences) have publically, at the meeting and/or later, each voiced concerns with certain aspects of the document, as did the two chief toxicologists from the NCI and the FDA, who were intimately concerned with the issue (Drs. Guarino and Richman).

As per Dr. Crouts memorandum of 9 July 1981, the Division (HFD-150) is to accept the protocol for conduct of preclinical studies of cytotoxic oncolytic agents as presented by the Division of Cancer Treatment at the NCI/FDA meeting of 27 April 1981 and it is the responsibility of the reviewing pharmacologists and the supervisory pharmacologist to implement this directive regardless of our unaminous concern regarding such acceptance. It is in that light that my addendum is being written.

At our team meeting regarding IND 18,905 on 17 July 1981 I was selected to contact DCT regarding deficiencies noted by the reviewing medical officer and pharmacologist. On that date, with Ms. Lee Ripper, CSO, on the line, I spoke with Dr. Michael Lowe, Acting Chief, Toxicity Branch, DCT (see telephone memorandum). Basically, Dr. Lowe and I discussed the following six areas of concern, which will also serve to critique present problems with the protocol in general and this application in particular.

I: It was requested that reports of gross pathology should be made available for evaluation.

This information was to be made available in the original IND submission according to the new NCI protocol.

From information gathered in the telephone conversations with Dr. Lowe on 17 July 1981 and 21 July 1981 (see telephone memoranda) the dogs given single injections of TNP were sacrificed in January 1981 while those on the times five schedule were sacrificed in March 1981 thus under the NCI "April protocol" both the gross and histo-pathology should have been available to the Agency by this date. Further, as TNP, is a sangivamycin analog, we were concerned of cardiotoxicity, especially arrythmias; the IND commented on possible hepatoxicity and cardiotoxicity; and clinical chemistries were abnormal weeks after TNP dosing - all reasons we wished to review the gross pathology.

Dr. Lowe and DCT did respond to this request by submitting, in draft, the gross pathology tables from dogs treated with TNP. Unfortunately, the hand carried data reached the Division this morning, 23 July 1981, on day 29 of the submission and after Dr. Coulter had finished his pharmacology review. No summaries, or pathologists diagnosis, were submitted either from the subcontractor (Raltech) or from prime contractor (Battelle), one may presume because NCI had not reviewed the summaries yet.

Technically, the draft tables may be said to fulfill the protocol's requirement to submit gross pathology prior to phase I but we would hope that such delays would not take place again, nor that evaluations by sponsor and their contractors would be missing.

The most serious flaw, however, is that the gross pathology, by itself, is of scant usefulness without the supporting histology. It is a futile exercise to review this submission - with its myriad of findings, including much hemorrhaging of various organs especially the heart; with its hints of possible hepatotoxicity, neprotoxicity, and even pancreatic toxicity - and attempt to interpret these data.

II: While some of these findings may be nothing more than agonal events, can we do little but guess. Obviously, NCI has guessed, since they have decided that they "have no current plans to conduct special studies of the cardiotoxicity or hepatotoxicity of NSC-280594 TNP). Such studies would be considered if there are any clinical (underlying mine) indications of unusual or unmanageable toxicities." (See July 22, 1981 submission to IND from Michael C. Lowe, Ph.D.). That statement answered my query during the 17 July 1981 phone conversation, as whether such studies were being planned, as per protocol provisions and commitments. A discussion as to what triggers special studies is needed in any final document since it now is obviously open to various interpretations.

III: The third item in my telephone conversation with Dr. Lowe concerned histopathology.

> We agreed that the protocol did not require that histopathology be submitted prior to phase I under the present protocol but that if it were available and pertinent then good science and common sense dictated that it be made available. I particularly was concerned with this compound's ability to cause abnormal clinical chemistries weeks after dosing.

Histology would be of great usefulness to check on the reversibility of toxicity i.e. were cells regenerating in the liver and repair occuring in other target organs, or, were we still seeing evidence of ongoing cellular destruction such as vacuolization.

Apparently the histology had been completely read, as I had predicted and as called for by the new protocol (sixty days after the last sacrifice) but it was not submitted today as I had hoped it might be. It is distressing not to have these data to evaluate when it is available but, as per directive, this is not an issue on which to base a clinical hold.

IV: Today's submission responds to my request to explain the mechanism of deaths seen in the toxicity studies by noting that:

> "the clinical observations made on dogs dying early...are included in the Phase I report already filed with the INDA."

Our colleagues at the NCI have difficulty in understanding the subtle difference between clinical observations and signs, colorful though they were with this compound (e.g. green feces, black feces, red streaked feces, orange urine) and mechanisms of death. At this point in time we still are unaware as to what caused the deaths of the animals on study.

V: The question or the rationale for a 24 hour infusion was raised at last Friday's team meeting and subsequent conversation with Dr. Lowe. Todays amendment referred us to the M.D. Anderson protocol (DT 81-39, 5.2, page 6) in the IND submission which states:

> "The 5 day dose schedule was selected because of the apparent superiority of daily administration over single dose administration in animal tumors. Although TCN-5'-PO_4 is very soluble, the parent compound TCN is not. Since it is possible that TCN-5'-PO_4 may be converted rapidly to TCN in the blood, it seems reasonable to give TCN-5'-PO_4 by continuous infusion in order to avoid high peak serum concentrations."

> While I do not find this rationale without some merit and while I understand that continuous infusion is a schedule many at M.D. Anderson seem to feel is less toxic under some circumstances (Benjamin's presentation at the ASCO/AACR meeting in April 1981 in which he presented evidence that Adriamycin myocardial toxicity may be reduced by this technique) this is not always the case, for example MTX toxicity may be increased.

VI: Finally, we discussed the Agency's concern regarding initial proposed clinical dose. My suggestion, as discussed with Dr. Crout and the reviewers of this IND, was to base the initial dose on 1/3 the "TDL" in the dog - the most sensitive species - as called for in the new protocol rather than on 1/10 the LD_{10} in the mouse.

Drs. Lowe, Abraham, and Hoth all have been in contact with me regarding this poinr and all seemed quite ready to accept 10 mg/m^2 rather than 30 mg/m^2 as the initial dose based on the considerations in the paragraph above. This was confirmed in an amendment to the protocol dated July 22, 1981 from Dr. Penta.

Why NCI did not spontaneously determine to base initial clinical dosage at 1/3 the approximate TDL in dogs is of concern to me.

Summary: For the reasons outlined above the amendments offered today by the NCI technically corrected many of the deficiencies by which this submission deviated from the new protocol, with the possible major exception of the lack of any plans to hone in on specific models of organ toxicity based on findings in the preclinical studies to date. At the 30 mg/m^2 X 5 dose in the dog, the observed toxicity appears reasonable, under the limitations imposed by the guidelines, for extrapolation to the initial clinical dose.

As the submission was initially submitted I concur in toto with Dr. Coulter's recommendation for a clinical hold as exemplified by our safety review which did recommend a clinical hold. As amended I feel it corrects, technically, most of the deficiencies on which we based our recommendation for clinical hold with the ambiguity as regards specific organ model toxicity studies before or after clinical trials, an area requiring clarification.

For the record, I wish to state that the protocol which I am being asked to implement is unsound and that I am severely distressed by the necessity of having to implement it. Several members of my staff appear to be even more distressed than I, as evidenced by their continued recommendations for a clinical hold (see memo of team meeting of 24 July 1981 prepared by Dr. Jerussi). We all agreed that this initial submission under the new guidelines was not up to the standards that the NCI can and should be able to prepare. Hopefully, this critique and the other reviews will aid the NCI to better prepare their future submissions.

This submission seems to bear out the "jerry-built" nature of the protocol and the problems of attempting to ascertain the target organ toxicities without the focus brought about by the availability of histology. My agonizing is compounded by the thought that the target population, phase I oncology patients, stand to benefit so little in the way of efficacy, although "therapeutic intent" is always a hoped for occurence. Yet, they may suffer a great deal of toxicity from the treatment. One hopes the ends (a cure for cancer) do indeed justify the means employed.

Now that I have indeed had an opportunity to review the first IND to employ the new protocol, and after deep thought concerning requests that I draft FDA guidelines for cytotoxic drugs, I feel I must not be associated with the actual drafting. My staff and I will be available for commenting on them of course.

Dr. Lowe tells me he is preparing a paper for publication regarding the new NCI guidelines and between that paper, his protocols handed out in April, and the proposed protocol I submitted to the Bureau in April 1981, the drafting shouldn't be a major hassle although I urge that FDA not publish. I wish to thank Dr. Crout for his understanding of my predicament in this matter.

David J Richman
David J. Richman, Ph.D.

cc:
Orig. IND 18,905
HFD-150
HFD-180
HFD-1/Dr. Crout
HFD-100/Dr. Finkel
HFD-102/Dr. Glocklin
HFD-150/DJRichman:7/23/81:7/24/81
HFD-150/CSO/LRipper
F/T:jb:8/11/81:Wang #5038A(13)

8/31/81

Senator HAWKINS. Ms. Ripper, you have served as consumer safety officer with your division since January, and you are responsible for liaison with the NCI and drug companies who sponsor these drugs; is that correct?

Ms. RIPPER. Yes.

Senator HAWKINS. I understand that several weeks ago, you were given an assignment to review volume upon volume of the NCI's drug submissions to the FDA. Would you tell us who gave you that assignment?

Ms. RIPPER. The Associate Director of the Bureau.

Senator HAWKINS. The Associate Director of the Bureau. Would you pull the microphone a little closer? You have such a soft, nice voice. What were the reasons given for the necessity of this laborious task?

Ms. RIPPER. We had received a Freedom of Information Request from the Washington Post to review all our files on the National Cancer Institute's submissions, and I was asked to make an administrative review of the IND's which had been prepared for them to come in and see and determine what problems there were; what sorts of adverse reactions had come up with the drugs; was there anything that had not been reviewed; what requests had been made that had not been answered, et cetera.

Senator HAWKINS. Did you find in your review any matters that may have slipped through the cracks at either NCI or the FDA?

Ms. RIPPER. I think on most of the IND's, you can find problems like that.

Senator HAWKINS. IND's, you found problems?

Ms. RIPPER. Yes.

Senator HAWKINS. Could you give us a few examples?

Ms. RIPPER. Well, on some of them, we do not get annual progress reports like we should. IMPY (pyrazalo-imidazole) was one of the ones that I specifically found. We have not received any submissions at all to this IND for over 2 years.

Senator HAWKINS. For over 2 years?

Ms. RIPPER. Right; no submissions at all—not protocols, results of studies, annual reports, or anything. There are other studies where we had asked for manufacturing and controls information, to be submitted before the studies proceeded past the phase I studies, and that information has never been submitted.

[Information supplied for the record follows:]

10/8/81

IND 3,859

Streptozotocin (Streptozocin) (STZ) (Zanosar)

IND received from NCI on March 3, 1967

Phase III (mostly combination studies)

Volumes 5.1 through 11.1 are in the Division
Volumes 1.1 through 4.1, 8.2 through 8.4 were sent to FRC (8.2 and 8.3 were open volumes)

The original reviews noted that in animals the drug showed hepatotoxicity, renal toxicity and diabetogenic effects. However, there was a surprising lack of toxicity on bone marrow and GI mucosa. In high doses the hepatotoxicity was irreversible; effects on renal functions were unpredictable at all doses and sometimes lethal; and the animals recovered slowly, if at all, from the diabetogenic effect. Low priming doses of STZ seemed to protect against the diabetogenic effect and nicotinamide given before or shortly administration of the drug prevented the diabetogenic effect without affecting the antitumor activity.

The January 1974 Clinical Brochure notes a published report by Broder and Carter on toxicity in patients with pancreatic islet cell CA. 5/46 patients (11%) had fatal renal toxicity; 30/46 (65%) renal toxicity; 33/49 (67%) liver function abnormalities; 11/52 (22%) insulin shock with hypoglycemia; 10/50 (20%) hematologic toxicities and 45/48 (94%) nausea and vomiting.

The great majority of the submissions consist of study group and independent protocols. The first comprehensive annual report is dated May 12, 1976. Of 392 evaluable patients (20 tumor types) only islet cell patients showed any complete remissions (17% + 35% PR). The report also notes that STZ is being used in a number of combination studies due to its low myelosuppression and "potential for efficacy."

Subsequent annual reports were based solely on studies in the past year and are mainly comprised of individual study summaries. There has been no effort to combine the data per cancer type for all studies to obtain a big picture of effectiveness and adverse reactions.

Orig. IND 3,859
HFD-150
HFD-150/LRipper
F/T:jb:10/8/81:Wang 5566A(16)

10/8/81

IND 10,905

Neocarzinostatin (NCS) (Zinostatin)

Received from NCI on August 19, 1974

Phase II

The initial reviews noted (1) various medical and chemistry deficiencies that need to be addressed before Phase III; (2) renal toxicity was dose limiting in animal studies and could be either acute or delayed even after very low doses; azotemia was progressive and irreversible; (3) dosage should be lowered to 1/3 TDL.

This IND is for NCS-K (manufactured in Japan) as opposed to NCS-B (manufactured by Bristol). K is 200-250X more lethal than B.

The IND was put on hold with requests for the change in dosage and more [redacted] chemistry information. ✓

Our response to their submission of December 16, 1975, stated that the chemistry was passable for Phase I studies only and again suggested that dosage be lowered to 1/3 TDL. Our Follow Up to Clinical Hold letter issued on October 28, 1975.

The hold was removed on February 3, 1976 in response to their amendment of December 16, 1975. Medical officer review notes that elevation of dosage and repeat dosage must be carefully monitored because of the late renal toxicity seen in the animal studies. ✓

A substantial amendment dated October 6, 1976 responded to the [redacted] chemistry deficiencies. Apparently it was never reviewed by a chemist. ✓

The first progress report was submitted March 2, 1978. It reported 7 U.S. Phase I trials. Out of 227 evaluable patients, there were 2 complete remissions (1%) and 9 partial remissions (4%). Some investigators reported that no nephrotoxicity was seen; others, that it is not dose related and is unpredictable. There is no medical officer review of this report. ✓

The annual report of January 19, 1979 reported on 204 evaluable Phase II patients. There were 1 CR and 19 PR (total of 10% response rate). Severe toxicity includes allergic reactions, especially after multiple courses, since NCS is antigenic and induces precipitating antibodies. Myelosuppression is dose-limiting and unpredictable, often delayed or prolonged. Pulmonary toxicity was seen in 4 patients.

The reports of 1980 and 1981 report similar results.

SUMMARY

Although animal studies predicted renal toxicity as the major dose-limiting toxicity, myelosuppression is seen as a larger problem clinically. Hepatic and renal toxicities are also relatively high. In addition, multiple courses are risky due to hypersensitivity reactions. There has been one death from cardiac arrest following the administration of the 6th dose of drug. Usually these reactions are controlled with IV fluids and steroids.

The ~~medical and~~ chemistry submissions of October 6, 1976 and January 7, 1977 should be reviewed if the drug ever goes into Phase III.

Presently NCS is considered promising only for leukemias and hepatomas.

cc:
Orig. IND 10,905
HFD-150
HFD-150/LRipper
F/T:jb:10/8/81:Wang #5564A(16)

8/10/81

IND 1,226

Mercaptopurine-6 (6-MP) (Purinethol)

Received from NCI on September 18, 1963

Volumes 1.1, 2.1, 3.1, 4.1, 6.2, 6.3, 6.4 have been sent to FRC (apparently 6.2 and 6.3 were open volumes)

There is an approved NDA 9-053 for the oral form of 6-MP. This IND covers Phase III I.V. studies for leukemias and histiocytosis.

Volumes 5.1, 6.1 and 7.1 contain protocols for combination use and 3 annual reports - dated February 1978, November 1979 and April 1981. There are no medical officer reviews for these in the jackets or the Division File.

The drug is mainly being used in the POMP regime - 6-MP, vincristine, methotrexate and prednisone. NCI states that the IV form of 6-MP is at least as effective as the PO form with an identical spectrum of toxicities. Its main superiority is that it can be given to patients unable to swallow the oral form.

Currently it is being used both to induce and maintain remission and for intensification therapy.

There does not seem to be any unusual or unexpected problem with toxicity.

The most recent medical officer review in the Division File is dated July 2, 1974. There are no reviews of any kind in the three volumes which are currently in the Division.

cc:
Orig. IND 1,226
HFD-150
HFD-150/LRipper
F/T:jb:10/8/81:Wang #5567A(16)

10/8/81

IND 13,953

Pyrazolo-Imidazole (IMPY)

Received from NCI on November 15, 1977

Phase II

Original pharmacology data showed target organs to be liver and kidneys in animals.

Our letter of March 13, 1978, noted numerous chemistry deficiencies and noted that they should be addressed before the studies are expanded from Phase I.

Progress report of January 1979 noted that they were nearing the end of Phase I and would be moving into Phase II soon. Only 1 (one) transient response had been seen during Phase I.

SUMMARY AND PROBLEMS

Except for some stability information, the progress report of January 1979 is the only submission in the jacket. It consists of 2 pages of prose, a one page table and some biopharmaceutics information. I cannot find the Division File or the Document History Card; MIS lists the January 1979 progress report as the most recent annual report. The medical and chemistry deficiencies noted in our letter of January 13, 1978 have not yet been answered. Apparently we have not sent them any progress report dunning letters.

cc:
Orig. IND 13,953
HFD-150
HFD-150/LRipper
F/T:jb:10/8/81:Wang #5563A(16)

10/8/81

IND 13,952

INDICINE-N-OXIDE

Received November 15, 1977

Phase II

The original pharmacology review notes that studies to determine accumulated toxicities produced dose-related toxicities including severe hepatotoxicity.

Deficiency letter of March 10, 1978, noted numerous medical and chemistry deficiencies.

Letter of June 29, 1978, Re: stability data dated February 17, 1978. "Please clarify the discrepancy in the reporting of one spot using paper chromatography for a product which has an appearance of dark yellow in color after 6 months of storage at 50°C." The University of Iowa replied that they "carefully re-examined" and found "a very light extra spot." The original paper chromatogram was included in the submission. The extra spot at 50°C which is not present in the RT sample is clearly visible. (In fairness, it could have darkened with age).

Chemistry review of November 28, 1978, notes chemistry deficiencies. Apparently no letter issued on this review. However, a chemistry deficiency letter of October 19, 1979, mentioned additional deficiencies. As of October 6, 1981, the medical and chemistry deficiencies do not seem to have been addressed by NCI.

June 8, 1979, amendment to master Phase II protocol was submitted. August 2, 1979, the Master Phase II protocol was submitted at our request.

Medical officer review of July 25, 1979, notes that at a Phase I Working Group Meeting, Dr. Kovach of Mayo reported that the Phase II recommended dose of 2250 mg/m^2/day x 5, repeated every 5 weeks, had shown itself to be unsafe in patients with prior nitrosoureas (NU) or mitomycin (M) exposure in their early Phase II study in patients with colon CA. They are not entering any more patients with prior NU or M exposure and plan to re-evaluate Phase I studies in these patients. Myelosuppression was especially pronounced in these patients. Letter on this to NCI issued August 7, 1979, also requested that the data from the Phase I studies at the Mayo be submitted.

Amendment of August 29, 1979, states all investigators have been notified of the Mayo findings and requested to exclude any patients with prior M or NU exposure.

NCI letter of June 24, 1980, states plan to proceed with 2250 mg/m^2/day x 5 q 5 weeks in patients with previous NU treatment.

Progress report of June 16, 1980, reports 2 possible drug related deaths from hepatotoxicity.

Amendment of August 20, 1980, implies a safe dose has been established for patients with prior mitomycin and nitrosoureas treatment but does not specify if it is that specified in the amendment of June 24, 1980, or if a lower dose has been chosen. To support this safe dose, minutes of two Phase I Working Group meetings and two New Drug Liaison meetings are included. However, the only data in these minutes on the x 5 schedule is from the Mayo Clinic in which it is stated that both Drs. Moertel and Kovach feel very strongly that a starting dose of 2250 mg/m²/day x 5 q 5 weeks for patients previously treated with M or NU is unsafe. They also state they are not testing lower doses because they do not feel they would be effective.

By telecon on September [illegible], Dr. Johnson requested Dr. Luz Hammershaimb, NCI, to obtain and sub[illegible] more detailed information on the M and NU pretreated patients. (FDA again requested [illegible] information by letter on May 7, 1981). On January 5, 1981, Dr. Johnson again called Dr. Hammershaimb. She indicated that she had not pursued the matter because no drug was available for the studies.

Amendment dated January 23, 1981, submits a Phase I protocol at doses beginning at 3000 mg/m²/day/ x 5. Prior treatment with M or NU did not exclude patients. Medical officer review dated May 5, 1981, did not question protocol.

On May 5, 1981, Dr. John Penta, NCI, reported to Ms. Ann Greenstein a total of three deaths at 2 cooperative centers. Studies at these 2 (but apparently not at a third coop center) were halted pending review.

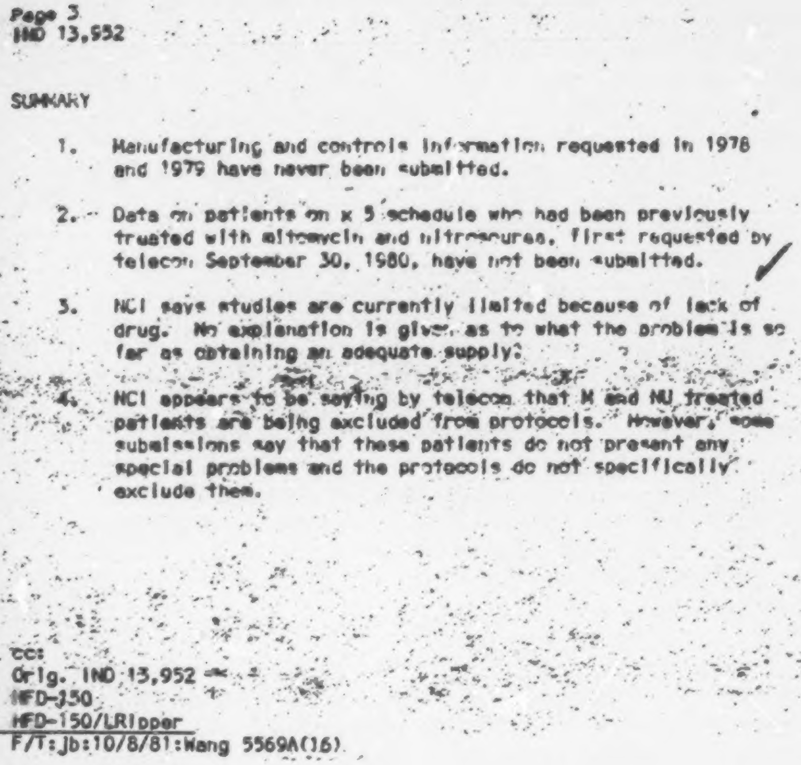
The annual report of July 6, 1981, notes that 15 of 114 patients in Phase II trials had drug-related hepatotoxicity with 6 patients, "less than 5% of the total population," being possible drug-related fatalities.

July 8, 1981, telecon Dr. Hammershaimb calling Dr. Johnson. NCI reopened the children's studies without consulting FDA. They plan to better define MTD by age group. She also reported one fatality--hepatic coma after one course of 3 g/m²/day x 5.

✓

July 30, 1981, amendment revising one of three protocols submitted January 23, 1981. Patients with liver metastases and elevation of liver enzymes are excluded from single dose schedule.

August 13, 1981, telecon, Dr. Johnson calling Dr. Hammershaimb to communicate that the July 30, 1981, amendment should also exclude patients with prior or present testosterone, progesterone and estrogen therapy. He stated she has not yet been able to get any more information on the patients with prior NU treatment. These patients are currently being excluded.



Page 3
IND 13,952

SUMMARY

1. Manufacturing and controls information requested in 1978 and 1979 have never been submitted.

2. Data on patients on x 5 schedule who had been previously treated with mitomycin and nitrosoureas, first requested by telecon September 30, 1980, have not been submitted.

3. NCI says studies are currently limited because of lack of drug. No explanation is given as to what the problem is so far as obtaining an adequate supply.

4. NCI appears to be saying by telecon that M and NU treated patients are being excluded from protocols. However, some submissions say that these patients do not present any special problems and the protocols do not specifically exclude them.

cc:
Orig. IND 13,952
HFD-150
HFD-150/LRipper
F/T:jb:10/8/81:Wang 5569A(16)

Senator HAWKINS. Did you report your findings to your supervisors?

Ms. RIPPER. Yes; I did.

Senator HAWKINS. What did they tell you to do?

Ms. RIPPER. They asked me to contact the Cancer Institute and to initiate action on the ones which needed division review.

Senator HAWKINS. What is your opinion regarding the relationship between the FDA and the NCI?

Ms. RIPPER. I have received the opinion that although we are supposed to treat them equally, we do treat them a little bit nicer than we do the drug companies. We tend to go a little more gingerly. For instance, we write them for a progress report, they get a nicer letter than the drug companies get.

Senator HAWKINS. What do they say, "Please"?

Ms. RIPPER. Something like that.

One of the largest differences in matters that I am concerned with is putting clinical holds on the studies.

Senator HAWKINS. They do what?

Ms. RIPPER. Put a clinical hold on a study. When the INDs are first submitted and we do the initial review, if it is felt that there are immediate safety problems such that the study should not be initiated at all, we put it on clinical hold. This normally is a decision of the team leader of the reviewing team, which is made up of a medical officer, a pharmacologist, a chemist, and myself. The medical officer, the team leader, makes the decision that it should go on hold, and then it goes through the supervisory medical officer and the division director, and then we call the sponsor and put them on hold.

However, with the NCI INDs, we are not allowed to put a study on clinical hold unless the Associate Director of the Bureau concurs.

Senator HAWKINS. Could you briefly give us a status report on an anticancer drug that my staff ran across in the files known as Jim's Juice?

Ms. RIPPER. Well, this is something that has come up as a result of our policy of giving out compassionate IND's. Normally, when an IND comes in, it is for a large study—at least 20 patients—and it consists of the manufacturing and controls information, pharmacology, that is all the preclinical studies, the clinical information, the protocol, the background of the investigator, the statistical methods that will be used to review the data. However, about 1962, a decision was made to allow compassionate IND's. That is, when a drug is in the Phase III part of the drug studies, and it is considered that we have a fair amount of information about it in patients, but sufficient data has not been accumulated yet to allow it to go into the new drug application stage, we allow individual physicians to treat one patient on an emergency basis when they state the patient has been refractory to other methods, or they feel this is clearly the drug of choice.

Now, in the summer of last year, 1980, we started receiving a number of phone calls from patients and patients' families, requesting the use of something called Jim's Juice. At that time, we started trying to find out something about it. We granted one IND to a patient who was said by his doctor to be a terminal patient. We also managed to find out who was making Jim's Juice, and we requested the field to do an investigation. When the person who was making the Jim's Juice found out that he was going to be inspected, he responded by saying that he was closing down his operation and in the future, would only make enough for his own personal use, his own personal studies, and for animal studies. However, we subsequently started receiving more requests for emergency IND's. We did grant a few, only for patients who were stated to be terminal patients, maybe half of whose physicians stated that the patient had already obtained the medicine, the drug, on their own, and they were already taking it. So in the end, I believe we allowed eight IND's to go out.

Now, when I became the CSO on this drug group in May, I pulled the files, and I started calling up physicians to get reports on the patients. Most of them stated that the patient had taken the drug for a while, and some of them felt that it had helped their patient, others had not seen any effect at all. But the end result was the patients had died.

We requested another inspection this June, and this time the sponsor did allow the inspector to come in. Since he knew that he was legally distributing the drug under IND's, he allowed the inspector to come in and inspect his premises; he permitted her access to his files—very minimal files, but what information he did have. It turned out that he was manufacturing the stuff in various places in his home—his backyard, his back porch, the kitchen. He was not following any sort of good lab practice procedures.

We have subsequently had several meetings over it, and it was decided that we could not give out any more compassionate IND's for Jim's Juice; we would only allow an IND if a regular IND came in from the manufacturer.

The whole compassionate IND program with cancer drugs is very difficult. When you get a phone call from these patients or from their physicians, and they tell you that they are a terminal patient, and they have been told they only have a few months to live, and they have read about this drug that has been used in animals or has been used in Europe, and they know that it might not help them, but there is nothing else that they can take, and they ask why can't they take it, it is very difficult to tell them, "No, we cannot give you permission to do that."

The whole compassionate IND program, use of compassionate INDs in this drug group, is very difficult as to when to give them out and when not to.

Senator HAWKINS. Thank you, Ms. Ripper.

[The following material was supplied for the record:]

CERTIFIED

NOTICE OF ADVERSE FINDINGS

September 17, 1981

Individual

Dear Individual,

Investigator of this office visited you on June 25 and 26, 1981 and inspected your activities with respect to the manufacturing and distribution of an unapproved new oncologic drug variously called Jim's Juice, Croconic acid, JS-114, 126-F and other numbers.

Investigator inspection showed that you have not filed a notice of claimed investigational exemption (investigational new drug application) for the manufacture and distribution of this unapproved new drug.

Further, with respect to the manufacturing procedures you use, Investigator found that you are not complying with the requirements of the Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals, 21 CFR 211. A detailed written list of your deviations from the regulations was presented to you at the conclusion of the inspection.

In summary, you are not testing either raw materials or the finished drug product to assure that it conforms to appropriate standards of identity, strength, quality and purity. You are not keeping manufacturing records to document fully the manufacture of each batch of drug.

You do not have written specifications for raw materials, labels, and packaging components or for finished product including approval and rejection criteria.

There is no stability testing program for your product and no record that any stability testing has been performed on it.

Distribution records do not exist which show the name and strength of the product, a description of the dosage form, quantity shipped and the control or lot number of the product shipped.

You are not maintaining a complaint file for the product.

Further, the drug is being made in your home without adequate separation from other household activities such as cooking.

Please respond to this letter, in writing, within 30 days with a description of the corrective actions you plan to take to bring your activities into compliance with the law. Please direct your response to FDA Compliance Officer.

Sincerely yours,

Director, Compliance Branch, F.D.A.

9/17/81

cc: HFD-150
HFD-302
HFA-224
HFR-53

Memorandum of Telephone Conversation
between
', Compliance Officer, FDA
and
Lee Ripper, Consumer Safety Officer,
Division of Oncology & Radiopharmaceutical Drug
Products, HFD-150, Bureau of Drugs

Subject: Jim's Juice

Individual

On September 16, 1981 I talked to Lee Ripper to ask what the Bureau's evaluation of our Individual EIR of 6/25, 26/81 had been with respect to his manufacture of a cancer drug without an IND. Mrs. Ripper indicated that the Bureau had decided to not ask for any further follow-up on Individual. She said a decision had been made to not approve any more emergency IND's unless Individual first asks for a full IND with manufacturing information.

Mrs. Ripper also said that only 4 of the emergency IND's are still open and that they will remain open until the patients die.

On 9/15/81 I also talked to of the Division of Drug Manufacturing who told me his Division hadn't done anything with the report and essentially regarded the problem as an IND problem.

Compliance Officer, FDA

O: EF
cc: HFD-150
cc: HFD-302
cc: HFA-224
cc: HFR-53
cc:
cc:
cc:

ENTRAL FILE NO.: JD/TA: PHONE: (EMPL NO: GRP:

AME: Individual STREET:

ITY: COUNTY: STATE: DISTRICT

(CONTINUED) ENDORSEMENT

PLANS TO DISTRIBUTE THE PRODUCT TO INDIVIDUALS WHO OBTAIN EMERGENCY/COMPASSIONATE IND's FROM THE F.D.A. Individual INDICATED THAT HE WOULD TRY TO COMPLY WITH FDA REGULATION

F/U: 1) REFER REPORT TO THE BUREAU OF DRUGS FOR REVIEW (HF [illegible]

2) OFFICIAL ACTION APPEARS TO BE INDICATED RECOMMEND REGULATORY LETTER

3) REINSPECT ≅ 12/81

IGNATURE DATE: 7/13/81

ISTRIBUTION DPU (CGCS), MOR(CGCS), HFD-150, HFD-3?:

PAGE 2 OF 2

FORM FD 481(E)-CG (10/79) 1981

E ASSIGNED: 6 /81

TRAL FILE NO.: TA: PHONE: GRP:

E: Individual STREET:

Y: COUNTY: STATE: ZIP: ISTRICT:

ATED FIRMS: , at residence just for ordering chemicals.

ISTRATION: REG TYP ! MO/YR ! MO/YR ! MO/YR ! REG TYP ! MO/YR ! MO/YR ! MO/YR ! REG TYP ! MO/YR ! MO/YR ! MO/YR !

none

USTRY CODES ON THE OEI: 54

OTAL ESTAB. SIZE	I.S. RECEIVED	BUSINESS SOLD	PRINCIPAL EST TYPE	RECALL NO.	REFUSAL CODE
Ø	[✓ YES] NO	80%	M	Ø	Ø

AB. STATUS: CHANGES: NONE NAME ADDRESS OWNERSHIP SIZE PROD CODE EST TYPE
OTHER: NEW FIRM O/B INACTIVE NOT OEI REGISTRATION

AC	PROCESS (PRODUCT) CODE	EST TYPE	INSP BASIS	EMPL1 PC: 22 NO: 202 HD: 9	EMPL2 PC: NO: HD:	EMPL3 PC: NO: HD:	PRODUCT	PRIT Y	RESCHED DATE	CLASS	D.D. CONC
002	54YIL	M	M /	20			Inositol	/	12/81	B	B C
332	54YIL	M	M /	4			Inositol	/	12/81	Ø	B C

IPLES COLLECTED: one

IPLE# PRODUCT:

291-177 Inositol product (DRUG)

FOR CONVEY/SUPPORT FACIL INSP

TOTAL	# VAI	# OAI

DQUARTERS UNIT REFERRED:

FD 483 ISSUED: [✓ YES] NO

SON REFERRED

OTHER FED GOVT INSP OR GRADING:

SPECTOR'S NAME/SIGNATURE:

F.D.A. Inspector

ENPL NO. 202

ABLISHMENT-NAME: Individual

E-INSPECTED: 6/25,26/81 DATE ASSIGNED : 6 81

E ERED	PRODUCT -CODE	EST TYP	EST TYP	EST TYP	PRODUCT DESCRIPTION
25/81	54YIL99	M			Inositol, Combination RX Drug use, liquid.

FORM FDA 481(C)-CG (10/80)

6/25,26/81

SUMMARY OF FINDINGS:

Inspection of this Drug Manufacturer was done under 46.832 as per assignment TWX from HFD-322, and 56.002 Drug Process Inspections. The only product is a purported cancer cure called Entelev. There is no IND for the manufacture of this product nor is Individual registered as a drug manufacturer.

Previous inspection dated 6/25,27/80 was indexed NAI as Individual said that he was out of business, at that time and had no plans to continue.

Current inspection found Individual manufacturing and shipping his product interstate. The physicans being sent the product had Emergency I.N.D.'s. Inspectional observations included various G.M.P. deficiencies such as: no batch records; no QC or testing records or procedures; no raw material, container/closure, or labeling handling records or procedures, among other things. Individual principal remedy for these deficiencies was to contact an outside firm such as Company A . to manufacture the product. Individual said he would try to comply immediately, and will seek the advice of Mr. A, a former employee of Company A.

Any correspondence should be directed to:

Individual

HISTORY OF BUSINESS:

Inspection of this drug manufacturer was conducted as per assignment TWX attached (Exh. 1).

The previous inspection dated 6/25,27/80 was the first inspection of Individual operations. The result of that inspection was that Individual promised to discontinue manufacturing and shipping his product. Since he discontinued before the end of the inspection, no FD 483 was issued.

As assignment TWX indicated, the Bureau of Drugs has recently received several requests (which were granted) for Emergency Compassionate I.N.D.'s from physicians with terminally ill cancer patients. Apparently physicians have been receiving shipments of this product from Individual under those I.N.D.'s.

Individual claims that his product is for treatment of cancer. Previously, he stated that his product can also be used for Lupus and other Collagen diseases.

About 80% of the business is interstate but Individual sells none of his products so annual volume of sales is zero.

In examining some of Individual raw material receiving records, it was noted that many of them were addressed to Company B at the ---- Street address. Individual stated that he is co-owner of this registered partnership, the other owner being his wife, According to Individual the only reason this firm name exists is for the purpose of ordering chemicals. He stated that this has no connection with his manufacturing practices.

Individual is not registered as a drug manufacturer. He holds no I.N.D.'s or N.D.A.'s on his product.

PERSONS INTERVIEWED AND INDIVIDUAL RESPONSIBILITY:

Credentials were shown and Notice of Inspection issued to: Individual. . Individual was the only person interviewed during the inspection, as he is the sole operator. His wife, . , was present at times during the inspection but admitted that this was her husband's activity. The FD 483 was presented to Individual.

During the inspection, Individual stated that he was in close contact with Mr. A , a "friend of the family" (formerly Vice-President of Quality Control with Company A ; currently employed by Company C . Individual stated that " Mr.A is very involved with getting this thing off the ground" and is currently "making contacts" (ie: Company A an independant lab to "set up a place" for manufacturing this product. Individual indicated that at this point it will be in Mr. A hands. Throughout the inspection, Individual said that Mr. A was his advisor on FDA matters and how to follow regulations. At the termination of the inspection, Individual stated that he would immediately contact Mr. A. .

OPERATIONS:

Name of Product

The product had no formal name at the initiation of the inspection. It had been called: Jim's Juice.Individual's Formula, JS-114, The Juice, and Croconic Acid. Individual also called the product and variations of the same, 126-F and other numbers. During the inspection, Individual decided to name the product Entelev to remedy all the confusion and "add credibility to the product".

Entelev

Individual considers himself a researcher doing his part for humanity. As such, individual is continually reformulating his product and making up test solutions. The product that individual distributes to humans is reportedly, the same formula (consistent from batch to batch/person to person). Currently the formula given to humans is called 126-F. During the last inspection the formula was called 114. According to individual, 126-F is the same as 114 except that the old method (114) involved bubbling the mixture with an aerator and this one (126-F) omits that step.

Individual uses many of the test solutions for mouse studies (see that section for details). Reportedly, 126, 126-A, and 126-H which are used in the mouse studies are the same formula as the 126-F used in humans.

The inspection primarily dealt with the formula used currently in humans, (126-F).

Building

All manufacturing is done at individual's residence. The garage and laundry room are used for raw material storage; the laundry room and enclosed porch and back yard are used for manufacturing; the kitchen is used for pH testing; and the laundry and porch also store old unused and/or unlabeled chemicals in test batches. Records are kept elsewhere in the house.

These functions are done in individual 's home along with normal household functions. For example: cars, mower, etc. stored in the garage; and cooking, etc. done in the kitchen. See item of 3 of FD 483.

During the inspection, individual's wife was cooking chicken for dinner while the kitchen counter was set up for testing the product.

Manufacturing

Individual 's description of his actual manufacturing processes is vague. But he stated that everything he does is written in the master records he supplied me. Individual described his processes in relation to the chemical diagram as see in Exh. 2.

Basically there are four ingredients in this formula: Inositol, Nitric Acid, Potassium Hydroxide, and Sulfuric Acid. The Inositol is received from one company , the Potassium Hydroxide and Sulfuric Acid are received from one company , and the Nitric Acid is received from another company . Individual does not sample or test these raw materials in any way, nor does he keep an inventory or other records on these raw materials (See item 1B of FD 483). There are also no procedures describing raw material handling, (Item 2A of FD 483).

The product is manufactured in the following way. See Exh. 3 thru 6 for complete description. Inositol and Nitric Acid are mixed. This is done in individual 's back yard. The mixture is then boiled until it becomes very viscous. The product then resembles tar or, in individual 's words, molasses. This process is described in Exh. 3 and chemically diagrammed in Exh. 2 step 1. This process makes two pans of this mixture.

Potassium Hydroxide dissolved in water is added to one pan of the above mixture and boiled. This process is described in Exh. 4 and chemically diagrammed in Exh. 2 step 2A. Sulfuric Acid diluted with water is added to this mixture and mixed. This process is described in Exh. 5 and chemically diagrammed in Exh. 2 step 2B.

The other pan of the original Inositol/Nitric Acid mixture is then mixed with a mixture of Potassium Hydroxide and Sodium Sulfite and boiled. This process is described in Exh. 6 and chemically diagrammed in Exh. 2 step 3A.

The end products of step 2B and 3A (Exh. 2) are then added together to form Entelev, JS-126-F. This is a mixture of Di-Sulfate Ether of Di-Croconic Acid Ether and Di-Sulfite Ether of Di-Tetrahydroxy Quinone Ether. This product is a brown watery liquid.

Individual keeps no records of his batch by batch manufacturing processes or a record that the batch was ever made, (ie: there are no batch records). (Item 1A of FD 483.)

Another step shown in Exh. 2 as step 3B is reportedly used in one of the product variations. the process of which is described in Exh. 7. Also,individual said that step 2C in Exh. 2 is just what happens to step 2B in the body.

During the inspection, individual was in the process of making two batches. One batch had just the Inositol measured out into the two loaf pans. The other was in the form of the Oxidized Inositol product.

There was finished product of 126-F from the 4-81 batch stored in a plastic milk jug. This remainder of 4-81 was sampled in it entirety by me and submitted as C/R 81-291-177.

stated that he only makes one batch a month until June when he will make two, since the demand is higher.

The product may be stored in plastic jugs as mentioned before or it may be stored as stock solutions of the intermediate steps. Procedures for making up these stock solutions can be seen in Exhs. 8, 9, 10. Exh. 8 is the stock solution for the Oxidized Inositol product, (step 2 in Exh. 2). Exh. 9 is the stock solution for step 2B in Exh. 2. Exh. 10 is the stock solution for step 3B of Exh. 2. These stock solutions are stored in either glass or plastic jugs.

The finished product is packed into opaque plastic pint bottles with black screw on caps. The bottles are reportedly received from a person at a Foundation. . Apparently, this person gets these bottles through his firm, Service Tectonics Instrument. (For this person 's relationship in this operation, see Memo dated July 3, 1980.) No records or procedures for container/closure handling were not available, (Items 1B and 2A of FD 483).

Equipment

Equipment observed consisted of loaf pans, beakers, flasks, graduated cylinders, titration burettes, and a potentiometer. The equipment was not labeled and there was old test product and unused and/or unlabeled chemicals in the laundry room and on the porch, (Item 3 of FD 483). There were no procedures or records of equipment maintenance or cleaning, (Item 4 of FD 483).

Coding

Individual stated that since he made his product only once a month, he coded it by month, (ie: 4-81 is the batch made in April 1981). Now that here will be two batches in June, he may begin using some other type of code designation.

TESTING AND QUALITY CONTROL:

The only test done on this product are pH and a potentiometric test. pH tests are done at each step in the processing to control the product. The potentiometric test, which according to individual , measures its mV/pH is used as the final test to assure that the product conforms to individual 's specifications. According to individual , his specifications are plotted on a graph; the X-axis being the potentiometer reading and the Y-axis being the pH reading. The product is ideal when the graph runs at a near vertical line. Individual stated that this is the way he can tell if the sulfur bonds are attached to the material in the correct position. There are no procedures describing these tests (Item 2B and 2C of FD 483) nor are there any records of these tests (Item 1C and 1D of FD 483), for any batch produced.

LABELING:

The product is labeled with file folder labels which state only "JS-126-F BATCH *** SHAKE WELL". There are directions which are attached to each bottle by a rubber band. See Exh. 11 for these directions. This labeling does not contain the statement "CAUTION; New Drug-Limited By Federal (Or United States) Law To Investigational Use".

STABILITY TESTING:

The product is made monthly. One pint according to individual is a 50 days supply. For the most part, shipments consists of one bottle (See Shipping Section). Individual assigns no stability dates. He has done no stability testing, nor, does he have any program to access stability, (Item 6 of FD 483).

SHIPPING AND DISTRIBUTION:

Individual ships his product UPS. On one occasion he remembers shipping it Federal Express so it would get there quickly.

Reportedly, the product is not shipped unless the physician tells individual that he/she has an I.N.D. for it. Individual said that if a patient were to call wanting the product he would tell them to contact their doctor and have him/her apply for an Emergency IND from FDA. Individual stated that Mr. A advised him that this was the appropriate procedure to follow.

Examination of shipping and distribution records shows that the name and strength of the product, dosage form, quantity shipped and control number are not included (Item 5 of FD 483). Individual showed me what he said were all his shipping receipts for 1981, from UPS. Copies were attached to C/R 81-291-177. The affidavit attached to that C/R, a copy which is attached to this EIR as Exh. 12, explains these shipments. A total of 9 shipments are documented. It should be noted that individual may send his product directly to the patients or an intermediary if directed to do so by the physician. This is true for the case of , a patient of Dr. ; , father of a patient of Dr. ; and , and intermediary who has contact with a patient of Dr. . Reportedly, Dr. may have as many as 4 patients on the product. He has one IND.

As stated above, usually the shipments contain one pint bottle. This is the case with the 1981 shipments with the exception of Dr. (2 bottles), Dr. , (5 bottles in addition to those sent) and Dr. (5 or 6 bottles), according to individual . Reportedly, Dr. , affiliated with a hospital , was sent the product to conduct mouse studies. The product was labeled as JS-126-V but is reportedly the same as 126-F.

COMPLAINT FILES:

Individual has no complaint file or record of complaints; (Item 7 of FD 483). Individual said that the only complaints he has is that the product causes diarrhea. Although many of the patients die while taking the product, they are terminally ill at the outset. Individual receives no results of patient progression from the physicians. Although, he said his product works, especially in the case of brain tumors.

LABORATORY STUDIES:

Individual , funded by a Foundation (See memo dated 7/3/80) contracted a lab to have four studies done on his product and test products. Copies of the reports are attached as Exhs. 13,14.15, the dates of these studies are July 7, 1980; Jan. 29, 1981; and May 26, 1981, respectively. The test numbers used in the studies which correspond to the product shipped to patients are: 126, 126-A, and 126-H. Number 126 was tested in study #1 (Exh. 13) and 126A was tested in study #2 (Exh. 14). The fourth study report has not, as yet, been published. Basically each study reports that results were not significant by N.C.I. (National Cancer Institute) standards.

DISCUSSION WITH MANAGEMENT:

Discussion was held with individual throughout the inspection and when the FD 483 was presented to him.

Individual said that he would make every effort to comply. He said he could see that his records were inadequate and why he should keep the records.

Individual said that it would be to his advantage to contract with someone else who is familiar with working with G.M.P.'s. He stated that he would immediately contack Mr. A and ask him to arrange this. He said he would visit the labs and speak with them, but if that did not work out, he would have Mr. A talk again with owner of Company A to arrange manufacture of this product with that firm. Reportedly, Company A has promised to let them (individual & Mr.A) use his entire firm for the manufacture of Entelev for only $1.00. Individual said that these inspection results told him that "now is the time".

I told individual that he must apply for a regular I.N.D. to produce this product and that the Emergency I.N.D.'s did not cover his production and shipping. I told him that he should register as a drug manufacturer as long as he makes Entelev. I supplied with a Registration Form.

Individual said he would do whatever he had to and that Mr. A knows all about these things. He also asked me if he should stop making the product for now. I told him to wait for a letter from FDA.

Attachments:

FD 482, FD 483, FD 484

Exh. 1.	Assignment TWX
Exh. 2.	Chemical Diagram
Exh. 3/7.	Master Processing Records
Exh. 8/10.	Master Processing Records for Stock Solutions.
Exh. 11.	Directions for use (label)
Exh. 12.	Copy of C/R 81-291-177
Exh. 13/15.	Reports of Labs Mouse Studies

Investigator, FDA

7/7/81

TE ASSIGNED: 6/80 PRIORITY: DATE INSPECTED: 6/25, 27/80

TABLISHMENT NAME: Individual STREET ADDRESS: EKPL NO: 5

IONE: DISTRICT: CITY: STATE

NTRAL FILE NO.: JC/TA: COUNTY:

ENDORSEMENT

COMPLIANCE INSPECTION. CONDUCTED AS A F/U TO A COMPLAINT FROM THE State ATTORNEY GENERAL'S OFFICE CONCERNING THE DISTRIBUTION E AN ALLEGED CANCER CURE BY individual. THIS IS THE INITIAL DA INSPECTION.

Individual IS A PATENT LAWYER WHO HAS BEEN MANUFACTURING A HEMICAL PRODUCT ("CROCONIC ACID") WHICH HE HAS BEEN GIVING AWAY TO ERMINAL CANCER PATIENTS AS A CANCER CURE. Individual HAS ARRANGE OR SOME ANIMAL TESTING, AND THE Foundation. "(A GROUP OF PEOPLE PPOSEDLY CURED BY individual 'S PRODUCT) HAS ALSO SPONSORED ANIMAL TESTING individual APPARANTLY DOES NOT ATTEMPT TO DIAGNOSE DISEASE CONDITIONS ND HAS GIVEN THE CHEMICAL FREE-OF-CHARGE TO ANYONE WHO CLAIMS TO EED IT. PROMOTION IS MADE BY WORD OF MOUTH BY FORMER "PATIENTS" URING THE INSPECTION, individual DECIDED TO DISCONTINUE THE ANUFACTURE OF THE PRODUCT, BUT HE DID INDICATE THAT HE MIGHT "EXPERIMENT" WITH THE PRODUCT. individual HAD PREVIOUSLY SHIPPED THE PRODUCT IN INTERSTATE COMMERCE AFTER RECEIVING MAIL REQUESTS OR THE PRODUCT. THE PRODUCT WAS NOT AVAILABLE FOR SAMPLING URING THE INSPECTION

F/U: 1) FIRM IS INACTIVE

JUL 23 1980

2) MONITOR FIRM'S ACTIVITIES 12/80

NOTE: AN INVESTIGATION WAS ALSO MADE AT THE EN FOUNDATION AND IS REPORTED IN A MEMO DTD. 7/3/80.)

7/15/80

DIST: DPU(CGCS), DMK(CGCS), HFD-3[illegible], HFD-15[illegible]

DATE ASSIGNED: 6 /80 PRIORITY: DATE INSPECTED: 6/25,27/80

CENTRAL FILE NO.: CD/TA: PHONE: GRP:

NAME: Individual STREET:

CITY: COUNTY: STATE: ZIP: DISTRICT:

RELATED FIRMS:

REGISTRATION:

REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR
	/	/	/		/	/	/		/	/	/
	/	/	/		/	/	/		/	/	/

INDUSTRY CODES ON THE OEI: 54

TOTAL ESTAB. SIZE	I.S. BUSINESS RECEIVED	SOLD	PRINCIPAL EST TYPE	RECALL NO.	REFUSAL CODE
0	YES NO	0 %	M		1

ESTAB.STATUS: CHANGES: NONE NAME ADDRESS OWNERSHIP SIZE PROD CODE EST TYPE
OTHER: NEW FIRM O/B INACTIVE NOT OEI REGISTRATION

PAC	PROCESS (PRODUCT) CODE	EST TYPE	ANN VAL	EMPL1 PC: 2 NO: 202 HD: 9	EMPL2 PC: NO: HD:	EMPL3 PC: NO: HD:	PRODUCT	PRIORITY	RESCH DATE	CLASS	O.G. CONC
56002	5LYIL	M		27			inositol	[illegible]	[illegible]	[illegible]	[illegible]
										8	9

SAMPLES COLLECTED:
SAMPLE# PRODUCT:
none

FDA CONVEY/SUPPORT FACIL INSP

TOTAL	# VAI	# OAI

HEADQUARTERS UNIT REFERRED:

FD 483 ISSUED: YES NO

REASON REFERRED

OTHER FED GOVT INSP OR GRADING:
none

INSPECTOR'S NAME/SIGNATURE:

SUPV. INSPR'S NAME/SIGNATURE:

FOR

Inviestigator,FDA

PRODUCT LISTING

FE: EMPL NO. 202

STABLISHMENT NAME: Individual

ATE INSPECTED: 6/25,27/80 DATE ASSIGNED : 6 / 80

ATE OVERED	PRODUCT CODE	EST TYP	EST TYP	EST TYP	PRODUCT DESCRIPTION
/27/80	54YIL99	M			Inositol, combination RX Drug use. liquid.
/ /					
/ /					
/ /					
/ /					
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FORM FD 481(C)-CG (10/79)

EIR/ Individual

SUMMARY OF FINDINGS:

A complaint of quackery was received from the State Attorney General's office, , on 6/13/80. The complaint concerned a purported cancer cure manufactured by Individual called "80" or "114". The complainant, Detective Sgt. collected a sample which is reportedly sulfate polytetrahydroxy guanine polyçlonic acid. Individual reportedly makes verbal claims for curing cancer. Sergeant also reported that Individual's products are being promoted by a Foundation and that this foundation may be a sponsor for testing at two different research institutes.

On 6/24/80, I attempted to contact Individual at his office. and at his home, . Later that day, I reached Individual by telephone and made an appointment to meet with him at his office on 6/25/80.

Credentials were shown and a Notice of Inspection issued to Individual, on 6/25/80. Individual supplied me with the following information.

Individual stated that his main object was to get FDA to approve his product. Individual said that he personally makes the product which he believes is helpful in patients with cancer. He stated he believes his product works, if not always therapeutically, it gives the terminal cancer patient hope. Individual mentioned that in one case, "the juice" was effective in curing scleroderma.

Individual calls his product "The Juice". He also refers to it as and labels samples as "Croconic Acid". There may still be two (2) others around also, called: JS-890C and AK-1 although he doubts this.

Individual is a semi-retired patent lawyer. He is also a chemist and was a bench chemist for for awhile. He also in 1962-64 worked for a research lab.

Individual stated that "The Juice" was being used by about 600 patients until about 1 1/2 years ago (Nov. 1978) when he had a meeting with Dr. "V", (Dr.), Oncology Dept., hospital; Dr. , Oncology, Hospital and Co. A, (a manufacturing firm, the actual person was not identified). The physicians recommended animal testing. Individual then decided to cut back his supply to patients. Reportedly, the goal he set for himself was a phase-out to about 50 patients in two years.

Individual was not sure how many people are currently on "The Juice" but estimated the number to be around 150. Individual said that all his patients are terminally ill cancer patients, who for the most part, are under the supervision of a physician. Individual stated that he gives "The Juice" to the patients. He insists that he was giving "The Juice" to people to test his material and that he has used many different formulations over the years. He said that "The Juice" has been successful, he feels, in curing cancer.

The only results he has of the effect of the material on humans are oral reports that the patients "feel better" or that their doctor told them the were "getting better", "the tumor went away", or, "they were cured". He does not correspond with all the physicians nor does he review patient charts.

The method of distribution is by pick-up personnally at his home or by mail. Individual said that he has patients throughout the USA and that he mails the product to them.

Individual stated that he has done animal studies. When questioned, further, he said that a foundation finacially sponsors animal studies done at a research institute. The Foundation is headed by a good friend and ex-patient of Individual 's. Reportedly the Foundation gives no money for Individual 's human studies. Individual manufactures "The Juice" for the Res. Instit. and delivers it to them. Reportedly he is not paid by anyone for this material. When Individual feels it's time for another animal study he stated that, he will/ask the Foundation to fund the Insitiute. Individual stated that, now, he is the only manufacturer of "The Juice". In the past, (8 moths ago) Co. A made it about four (4) times, for shipment to the Institute and another company for animal tests only. Reportedly, Co. A also tried tableting and encapsulation. Co. A 's involvement was discontinued as they (Co. A) ceased manufacturing operations.

Individual reportedly manufactures the material in the following way.

Inositol (from one lab) and Nitric Acid (from another) are combined and heated to 100°C in a bowl. Once combined, the solution is put into a gallon jug and bubbled (with an aquarium airator). Sodium sulfite is added at this step and bubbled for twelve (12) hours. Individual bottles are labeled as "114" "SHAKE" only. Individual said that he prescribes 300 mg-600mg daily depending on the patient.

Upon further questioning, Individual indicated that, although the basic formula was the same; ingredients may be used in various quantities and several different ingredients may be added at any time.

I informed Individual that I wished to inspect his manufacturing facilities at his home that day (6/25/80). A conversation ensued on whether FDA had jurisdiction over his operations. I read the FD 482 to him and we discussed it. Individual stated that he did not want me to have access to his patient names and therefore refused to have me review his distribution. He stated that he was afraid to let me in the door for fear he might be forced to turn the names over to me, like criminal law demands. I told him that he could refuse any portion of the inspection he wanted, but he said he wanted to sort through his things before I saw them and that he wanted to consult some experts. Therefore, he was refusing me inspection until further notice. Individual also stated, as of now, he would stop all interstate shipment for humans.

I telephoned Individual on 6/25/80 to reassure him I didn't want patient names. He agreed to meet me at his home on 6/27/80.

On 6/27/80, I visited Individual 's home in an attempt to conduct a GMP inspection of a drug manufacturer. Upon my arrival, Individual briefly showed me around the premises then asked me to let him tell me the changes he had made in the past two days.

Individual said that he spoke with many people during the last two days (he would give me no names) three of which were "experts" in my field (meaning FDA). He stated that these "experts" told him that FDA did have jurisdiction over his product and that he would have to follow the GMP's, and that if he decided to discontinue manufacturing, he should take all measures to convince me (FDA) of that.

I asked Individual if he was familiar with IND procedures. He said that he knew all about them. I also reminded him that if he were to continue making his material he would have to register as a drug manufacturer.

Individual stated that, because of the (above mentioned) advice, he, as of two days ago, discontinued any manufacturing, for either animal or human use. He said that his kitchen used to be the manufacturing area but, he threw away all the manufacturing equipment, containers and product on hand. He said he threw it out with the garbage. Reportedly, he also destroyed all records of manufacture, receipt and distribution. This subject was discussed at quite some length. Individual said that he had already begun turning away patients.

He stated that he was still going to "experiment" with his product. By experiment he meant, making it in minute quantities for his use only for chemical testing (i.e. pH, etc.). He admitted that he was "ready for a real breakthrough any day now" and that he would be testing (in vitro only) for any chemical changes. Individual has decided that he will apply for a patent and hope that some drug company will want his formula. Individual stated that recently a drug company (he would not give me the name) expressed interest in his product.

Inspection of the premises revealed that chemicals were stored in the laundry room and garage of his residence. A variety of chemicals was seen including Inositol and Nitric Acid. Also seen were about ten bottles of 4 oz. of fluid labeled "CROCONIC ACID". Individual said each bottle was a different sample solution for JS-114, as he is always formulating different solutions. He stated that all his materials were for his personal in vitro tests only. On the enclosed porch, Individual had his test facilities set up. Equipment consisted of a pH meter, titration tubes, beakers, etc. There were lab books, reference literature, charts and graphs in this area. Since it appeared that Individual had discontinued manufacturing his purported cancer cure, the inspection was terminated.

Individual also stated that he had been contacted by the press (newspapers, magazines, and televison) many times, but, he refused to disclose any information because he didn't "want this thing to get blown all out of proportion like laetrile".

It should be noted that throughout the inspection when Individual referred to his practices or decisions, he always said "we". When asked who "we" was, he stated that he was referring to what he jokingly calls his "board of directors". He explained that there is not a formally designated board of directors but there is a group of people with whom he consults when problems arise. The "members" names were not given to me, but Individual did say they were prominent physicians, the Foundation and others.

Attachments: FD 482, Notice of Inspection
Exhibits
Exhibit 1 through 6 are photographs.

F.D.A. Inspector
Investigator,

7/7/80

Individual

6/25,26/81 STX. EXH. 11

DIRECTIONS FOR USE

(Conc. = 100 mg./ml.)

SHAKE WELL. Take two (2) teaspoons of JS-126 and stir into about a pint of water (or coffee, tea, milk, etc. to suit the taste).

Drink the pint of mix over one day (for example, a swallow every 2 to 4 hours during the waking hours.)

It is recommended that intake of vitamin E be kept to a minimum.

This dosage level sometimes causes diarrhea. If this happens, and is excessively inconvenient, cut the dosage in half until the patient adapts to the material. Then try the recommended dosage again.

Refrigeration of the material is recommended to avoid mold growth.

If the material is frozen during shipment, let it thaw at room temperature and then shake well.

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Senator **Hawkins**. Senator Kennedy, the panel is yours.

Senator **Kennedy**. Thank you very much, Madam Chairman. I do want to welcome the members of the panel and thank you for your responses to the members of the committee.

Dr. Hensley, it is nice to see you back again. You have been helpful to the committee over a period of years, and we have always benefited from your insights.

Let me ask you, what is the nature or the relationship now between NCI and FDA? How would you characterize it—good, fair, poor—or have you got another one?

Dr. **Hensley**. I think the relationship right now is strained. On the one hand, I think NCI, no matter what is on paper, probably has very little inclination to be regulated, and I think FDA, certainly FDA management, has very little inclination to regulate.

I think you have to ask yourself, since these are all reasonable people, and certainly since Bob Young, who is sitting here, is a very reasonable person and disagrees with both, why do they disagree. And I think the answer began to be explored in Representative Gore's hearing this past Tuesday.

To understand how reasonable people can take such widely differing positions and defend them so vigorously, you have to understand that all research is not the same. There is a spectrum of research that runs from nontherapeutic to therapeutic. Nontherapeutic research is the kind of research I used to do where we give experimental drugs to normal volunteers. Purely therapeutic research is basically what cancer chemotherapy is. Most cancer chemotherapists are treating patients; by coincidence or by matter of circumstance, they happen to be also doing research. For many of them, it is something of a technicality.

The regulations in the Food and Drug Act, which Bob has referred to, are very heavily weighted toward nontherapeutic research, toward the protection of the human subject. The reason that I so aggressively pursued methyl-CCNU, and the reason that I have come forth with the information today, is that in my opinion, NCI did not adequately protect human subjects. I do not think that necessarily relates to the Food and Drug Act and to the regulations and whether or not they ought to be regulated. I think that you have to ask the question—certainly, I have begun to ask myself the question—is it proper to apply the regulations, and in fact, the Food and Drug Act as it is presently written, to purely therapeutic research, which happens to include NCI. I personally do not think it is. Bob and I are both aggressively criticizing NCI, but I think we diverge 180° after you pass the point of protection of human subjects.

Senator **Kennedy**. I think that is an important point. I think there is probably some difference on the panel. I would be interested in your view, whether you think the experimental research drugs that deal with the cancer ought to be regulated differently than the drugs developed by pharmaceutical companies.

Dr. **Hensley**. I certainly do.

Senator **Kennedy**. Why?

Dr. **Hensley**. Because the research being done is purely therapeutic. Let us take a phase III study done by a drug company and compare it to a phase III study under NCI auspices. The drug company is most likely developing a "me-too", psycho-active or analgesic medication. They will profit from their research, and it is really an extension of the fee-for-service system. NCI, on the other hand, the doctors using those drugs, most of the time—not always—there are some notorious exceptions—but most of the time, are basically treating patients.

I think that historically, the rules governing research have drawn a distinction between nontherapeutic and therapeutic research, even going back to the declaration of Helsinki. That is basically my thinking.

Senator KENNEDY. Well, do I understand your position that you think that there ought to be more freedom, more latitude, less regulation?

Dr. HENSLEY. Only in some areas.

Senator KENNEDY. In the areas of cancer research.

Dr. HENSLEY. Well, only in some parts of that. If you stop and think about it, you have got the Department of Health and Human Services engaged in a "war on cancer," as they have. You have a right hand, NCI, treating patients and doing research, and you have got a left hand of the same body, regulating or attempting to restrain, or let us just say regulate, the right hand. In other words, the right hand and the left hand, rather than working together, are working in opposition.

One of the things I have noticed in the documents I have seen that Senator Hawkins' staff has developed is that FDA and NCI seem to have very little regard for one another—the staffs do. They often talk at each other, but very seldom to each other.

I would like to see the effort modified significantly. I would like to see the expenditures put forth by FDA and the expenditures put forth by NCI united under a single system of management. I cannot see why FDA and NIC cannot work together in some areas.

On the protection of human subjects, however, on the obligation to inform clinical investigators of adverse effects, there can be no compromise. Other things—let us say, how they establish the records, how they get their protocols approved, maybe even institutional review board regulation, I think can be handled differently, and perhaps the regulations can be rewritten to include, let us say, cancer chemotherapeutic drugs under that blanket term that Ms. Ripper has used, compassionate research.

Senator KENNEDY. Well, I think that is, at least, very much a part of the focus of these hearings today. You believe that it is vitally important that the adverse drug impact be reported promptly by the clinical investigators and that the information that is gained by NCI or the FDA with regard to adverse drug implications ought to be reported promptly to the investigators.

Dr. HENSLEY. That is correct. That is the most important thing, that it be looked for and reported. As Bob Young has pointed out, it very often appears that the people just are not looking; the data is coming in, and it is not being reviewed in a timely fashion, and the system is breaking down.

Senator KENNEDY. And your suggestions about how that can be assured?

Dr. HENSLEY. There is one simple suggestion that could be implemented with virtually no cost and in a short period of time. One of the gaping holes in NCI's monitoring of their clinical trials is in phase III. They have contracted in recent years, I guess over the last 2 years, for outside help to monitor phase I and II. Wouldn't it be nice if we could take inspectors like Investigator Mead, who is trained to review medical records, and permit them to, let us say, act as monitors for NCI. And there are systems that could be devised that would make that possible. We have hundreds of inspectors like Inspector Mead who could do that very job.

Senator **Kennedy**. But as I understand, part of your answer is that in terms of the clinical investigators themselves, they ought to be monitored?

Dr. **Hensley**. Oh, yes, very definitely.

Senator **Kennedy**. Can they do that job with four individuals, or how many monitors do you have now?

Dr. **Hensley**. Well, NCI has a staff of monitors, I think maybe six over there. Those people are, for the most part, 2-year fellows who rotate through. I do not think they are there because they want to be monitors. FDA has only three medical officers to handle the 80 or so IND's that those six monitors of NCI attempt to follow.

Most drug companies, rather than running a system like this, with six monitors trying to monitor 80 studies, establish a hierarchy They have a number of associate medical directors, as I once was, to whom report a number of assistant medical directors. The associates are responsible for, let us say, 30 or 40 percent of the clinical program each, and each of their individual monitors are responsible for a few drugs.

It would be nice if a similar system could be developed at NCI, and those associate directors be full-time, civil service-type employees, or PHS. That would provide continuity, and they could make use of their 2-year fellows to do the day-to-day, ongoing scoutwork, if you will, or the review of the documents as they come in.

Senator **Kennedy**. It is your sense that this could be handled from an administrative point of view? Obviously, from a number of personnel—I suppose you are talking about resources to be able to do this kind of monitoring and also a commitment by the agencies to do it. But is it your sense and feeling that that could be done under the existing statute, or do we need a change in the statute?

Dr. **Hensley**. We need a change in the regulations, and I think we could change the regs and keep the Food and Drug Act.

Senator **Kennedy**. Well, I would hope that we would be able to—not today—but be able to get some other recommendations from members of the panel in this area, so that we can try and be responsive to the points that have been raised earlier by a number of the individual witnesses and which I think are of common concern to all of us here.

Thank you very much.

Senator **Hawkins**. We want to thank all of you for coming today.

The next panel we have will be from the NCI. Dr. John Macdonald, Dr. Daniel Hoth, Dr. Silvia Marsoni, Mr. Paul Davignon, and Dr. Vincent Bono.

Would you stand beside your chairs, please, and I will swear you in? Do you swear to tell the truth, the whole truth, and nothing but the truth?

[Witnesses answer in the affirmative.]

Senator **Hawkins**. Let the record reflect the witnesses answered in the affirmative.

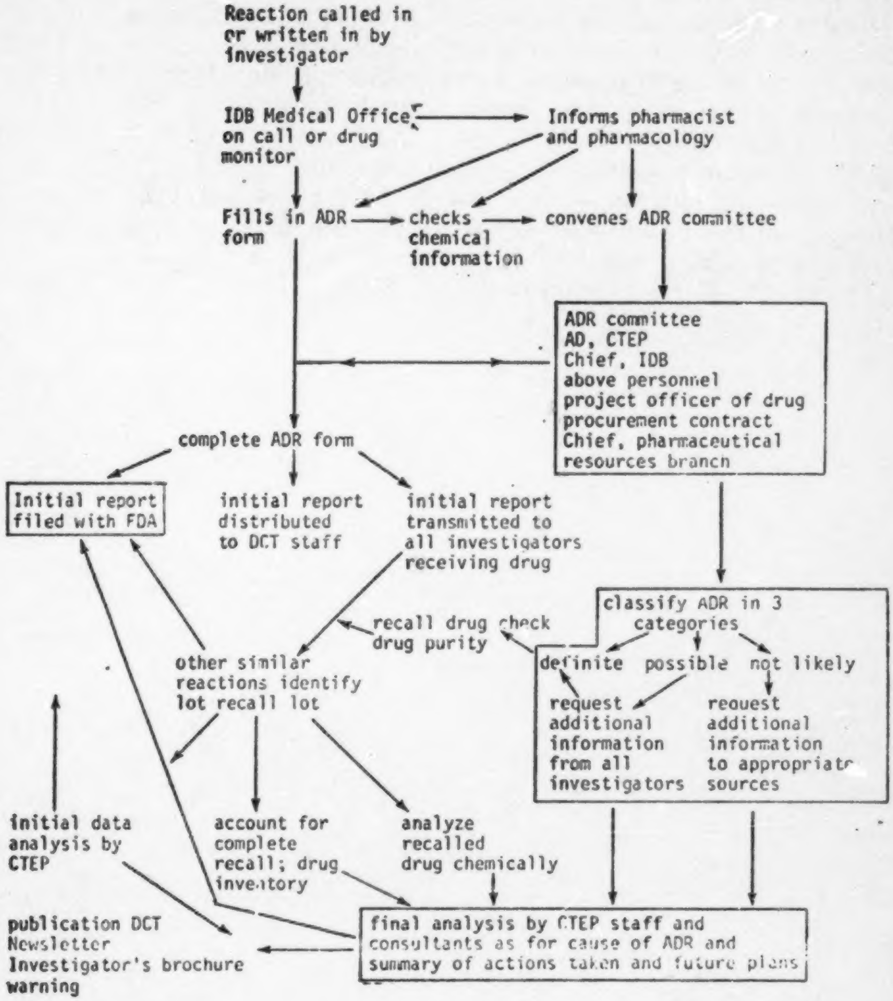
Please be seated.

Dr. John Macdonald is Associate Director of the Cancer Therapy Evaluation program. Dr. Hoth is Chief of the Investigational Drug Branch. Dr. Silvia Marsoni is a Supervisory Drug Monitor, and Mr. Davignon is Chief of the Pharmaceutical Resources Branch. Dr. Bono is formerly of the NCI; until the beginning of this year, he was Chief of the Investigational Drug Branch.

As all of you can see—some maybe better than others—we have mounted on the easel a flow chart of adverse drug reactions, called ADR by the professionals.

[The chart referred to follows:]

FLOW CHART OF ADVERSE DRUG REACTION (ADR)


Reaction called in or written in by investigator
IDB Medical Officer on call or drug monitor
Informs pharmacist and pharmacology
Fills in ADR form
checks chemical information
convenes ADR committee
ADR committee
AD, CTEP
Chief, IDB
above personnel
project officer of drug procurement contract
Chief, pharmaceutical resources branch
complete ADR form
Initial report filed with FDA
initial report distributed to DCT staff
initial report transmitted to all investigators receiving drug
classify ADR in 3 categories
definite
possible
not likely
request additional information from all investigators
request additional information to appropriate sources
recall drug check drug purity
other similar reactions identify lot recall lot
initial data analysis by CTEP
account for complete recall; drug inventory
analyze recalled drug chemically
final analysis by CTEP staff and consultants as for cause of ADR and summary of actions taken and future plans
publication DCT Newsletter Investigator's brochure warning

Senator **Hawkins**. Can any of you panelists tell us who dreamed this one up? When it was made part of the NCI official procedure? Dr. Hoth, we call on you first.

STATEMENTS OF DR. DANIEL HOTH, CHIEF, INVESTIGATIONAL DRUG BRANCH; DR. VINCENT BONO, FORMER CHIEF, INVESTIGATIONAL DRUG BRANCH; DR. JOHN MACDONALD, ASSOCIATE DIRECTOR, CANCER THERAPY EVALUATION PROGRAM; DR. SILVIA MARSONI, SUPERVISORY DRUG MONITOR; AND PAUL DAVIGNON, CHIEF PHARMACIST, PHARMACEUTICAL RESOURCES BRANCH, A PANEL

Dr. **Hoth**. Yes. This chart was included in a document we refer to as our "Drug Master File," in a subsection entitled "Operational Plans and Procedures for Clinical Trials," which was developed in January 1978.

I think it is particularly important to point out that we have updated our procedure in this area, and I would say that we are no longer using that flow chart.

Senator **Hawkins**. I do not blame you.

Dr. **Hoth**. I would like to submit for the record an update of our procedures in that area. On October 26, we mailed a letter to over 5,000 investigators around the Nation, reminding them of their responsibilities to report to us, and in addition, internally, we have changed a number of procedures, which I would be delighted to address specifics of.

[Information supplied for the record follows:]

October 26, 1981

TO: CLINICAL INVESTIGATORS

FROM: Bruce A. Chabner, M.D.
Director, Division of Cancer Treatment

The Investigational Drug Branch wishes to call attention to the importance of immediate reporting of adverse reactions among patients treated with investigational drugs supplied under an NCI held IND. The seriousness of this situation should not be underestimated. Not only are timely reports of adverse drug reactions (ADR's) required by FDA regulation (see attachment) but such timely reporting improves both scientific communication and patient safety by allowing the NCI to rapidly disseminate such new findings to the community of investigators studying that drug. In accepting responsibility for conducting investigational drug trials, we all are obliged to report adverse reactions immediately to the NCI (the IND sponsor) who will then pass on this information to the FDA. Our responsibilities in this matter are clearly stated in the investigator registration (Form FD-1573) which we all sign. (see attachment)

Therefore, the Division of Cancer Treatment, following a review of its policies in this area with its Board of Scientific Counsellors and the FDA, would like to reiterate its policy for the responsibility of investigators to report Adverse Drug Reactions. We are issuing the attached statement as a further clarification and to guide you in meeting your responsibility.

NCI

DIVISION OF CANCER TREATMENT

ADVERSE DRUG REACTION
WITH INVESTIGATIONAL AGENTS

Responsibilities of Investigators

The prompt reporting of adverse drug reactions (ADR) to DCT is the responsibility of each investigator engaged in clinical research with investigational drugs supplied by NCI. It is the policy of DCT that investigators are encouraged to submit such reports even if there is only a suspicion of a drug effect. Procedures for reporting ADR's are divided in two general catagories based on their severity and quality.

A) Any severe, life-threatening or fatal, toxicity should be reported immediately by telephone (grade 4 or 5 in most grading scales). This should be done even if that type of toxicity has previously been reported.

Initial notice of adverse drug reactions of this magnitude should be called to the IDB at 301-496-1196, which is available twenty-four (24) hours daily. As a follow-up, within ten (10) working days, a detailed initial case report should be sent to the Investigational Drug Branch (IDB), Landow Building, Room 4C-09, Bethesda, Maryland 20205. More specifically: 1) major organ toxicity (liver, renal, cardiac, CNS, PNS, skin, anaphylaxis) should be reported even if already previously reported in the clinical brochure in the annual report and in the literature. 2) Myelosuppression with a drug known to have that toxicity is only to be reported if it is clearly the major factor leading to death.

3) Fatal aplasias occurring in leukemic patients should be reported only if clearly related to the experimental drug (i.e. single agent trial) otherwise should be communicated through normal channels (see A.2.)

Investigators on protocols of Cooperative Groups should check with the Operations Office and/or the New Agents Committees Chairman about their practices for handling these reports, which may be routed through them, if a mechanism is in place to do that on an emergency basis.

B) Toxicities which are not fatal life-threatening or severe (i.e. "A" above) should be promptly reported in writing if that type of effect has not previously been reported, (i.e. any effect which is not listed in the clinical brochure or in the last Annual Report). For instance, if a patient develops dermatitis suspected to be related to an investigational drug, and dermatitis is not indicated in the clinical brochure or in the Annual Reports, then a report should reach the IDB within ten days of its occurrence.

In all instances investigators should be prepared to provide a full medical case report to NCI if requested. Any investigator who is dubious about whether a particular instance of adverse reaction needs to be reported should call the IDB at the above number.

Failure to report adverse reactions in a timely manner may result in discontinuation of the study, and, if severe, revocation or suspension of the investigators permission to perform clinical research using investigational drugs under NCI IND.

This reporting of adverse reactions is in addition to and does not supplant the reporting of toxicities as part of the report of the results of the research protocol (e.g. cooperative group minutes).

10/26/81

ADVERSE DRUG REACTIONS

FDA REGULATIONS

NCI RESPONSIBLITY

" The sponsor shall promptly investigate and report to the FDA and to all investigators any findings associated with the use of the drug that may suggest significant hazards, contraindications, side effects and precautions pertaining to the safety of the drug. If the finding is alarming it shall be reported immediately and the clinical investigation discontinued until the finding is adequately evaluated and a decision is reached that it is safe to proceed".

FD - 1571

INVESTIGATOR RESPONSIBILITY

"Any adverse effects that may reasonably be regarded or caused by, or probably caused by, the new drug shall be reported to the sponsor promptly, and, if alarming, it shall be reported immediately".

FD - 1573

Dr. HOTH. I might point out that this has been an ongoing process over a number of years and does not simply represent something that has happened in the last week.

Senator HAWKINS. You mean, the changing of the chart has been ongoing?

Dr. HOTH. Well, I think that the point that I would like to emphasize over and over again today is that Our entire approach to handling clinical trials with investigational agents has been an evolving process. I think that if you look at what was happening at NCI, and really in the drug industry in the early 1970's, there was a very different situation than we have now. I would be delighted to submit for the record another document, describing our evolution over that period of time. Our drug distribution has been tightened in a series of steps; our classification of drugs into those which are very experimental, the group A, versus those which have some benefit, group C, has been established. And I think that we have become increasingly aware of our responsibilities in the adverse drug area.

I think every time that we change the system, we find that there are new problems that are created by that change, and we have to modify that. So we look at it as a continuing evolution.

Senator HAWKINS. But at a recent meeting with FDA officials, you did describe this chart as "tortuous"?

Dr. HOTH. In a meeting in September—I believe it was September 1—with Dr. Crout and his staff at the Bureau of Drugs, we described our revisions in this document that I would like to submit. There were two subsequent followup meetings, with Dr. Kelsey's staff in the Division of Scientific Investigations.

[Information supplied in the record follows:]

MEMO OF MEETING

FDA - NCI

September 1, 1981

Attendees:

NCI: Dr. John MacDonald, Associate Director for Cancer Therapy Evaluation Program
Dr. John Driscoll, Acting Director, Developmental Therapeutics
Dr. Dale Schumacher, Regulatory Affairs
Dr. Ted Gram, Supervisory Pharmacologist
Dr. Saul Schepartz, Deputy Director, DCT
Dr. Daniel Hoth, Chief, Investigational Drug Branch
Ms. Ruth Davis, Toxicology Branch
Dr. Michael Lowe, Toxicology Branch
Dr. Bruce Chabner, Chief, Clinical Pharmacology Branch

FDA: Dr. Richard Crout, Director, Bureau of Drugs
Dr. Marion Finkel, Associate Director for New Drug Evaluation
Dr. William Gyarfas, Director, DORDP
Dr. David Richman, Supervisory Pharmacologist, DORDP
Dr. Howard Walker, Oncology Group Leader, DORDP
Dr. Frances Kelsey, Director, Division of Scientific Investigations
Dr. A. W. Coulter, Pharmacologist, DORDP
Dr. R. S. K. Young, Medical Officer, DORDP
Ms. Lee Ripper, Consumer Safety Officer, DORDP
Dr. Alan Lisook, Chief, Clinical Investigations Bracnch, DSI

Subjects of Meeting:
1. Revised Toxicology Guidelines
2. Monitoring of Clinical Trials
3. Accountability for Drug Distribution
4. Reporting of Adverse Reactions
5. IRB Approval for Group C Drugs and Special Exceptions
6. Tricyclic Nucleotide IND 18,905

1. Revised Toxicology Guidelines

After introductions, Dr. Finkel began the meeting by stating that the Bureau has made recommendations to the Commissioner on the toxicology protocol and his memo containing his opinions is expected to issue soon.

NCI representatives distributed a report on retrospective comparison of mouse vs. human MTDs. FDA asked if NCI would recommend changes in the guidelines if they weren't satisfied with the predictiveness of the mouse model. Dr. Chabner agreed that they would for the common types of toxicities.

Dr. Crout commented that there were no cases on the list where the mouse was more sensitive than humans; however he thought he remembered some instances (perhaps from the older literature) where the mouse would not be the more sensitive. Dr. Richman questioned the reproducibility of the studies. Dr. Crout commented that he remembered older info on about 40 drugs of which in 5-6 one-tenth the mouse LD_{10} would be too high for humans.

As to when histopathology will be submitted: Dr. Chabner thought they could send both species (mice and dogs) within 90 days of filing the IND. This would mean only 60 days after the initiation of clinical studies and, therefore, if any problems were found as a result of the histopath examination, the clinicians would only be 1-2 steps into the protocol. Dr. Finkel stressed early submission of the histopath since this could mean less clinical monitoring would be necessary.

Dr. Richman mentioned that the April protocol states the histopath will be submitted to NCI from the contractors 60 days after sacrifice; therefore, he questioned why NCI can't submit it to the FDA sooner. Dr. Lowe explained that only a draft is submitted at this 60 day timepoint. It must go back to the contractor, be signed by QL, finalized, returned to NCI, finalized, reproduced, etc. Dr. Richman said that if only raw data was available at the time of submission, FDA would prefer raw data to no data.

Dr. Crout emphasized that the histopath information is important first to the investigator, second to the NCI and only thirdly to the FDA. Dr. Finkel concluded by stressing that the histopath should be submitted as soon as it is available, NCI should not wait for the 90 day post submission time point.

Dr. Richman asked what would trigger special studies and what would these special studies be. Dr. Lowe responded that anything untoward, any toxicity not anticipated would call for special studies. Dr. Richman asked if the arrhythmias seen with homoharringtonine would qualify under this criterion. Dr. Lowe answered that they closely monitored the dogs and since the problem seemed to be dose-related they did not plan any additional studies.

Dr. Chabner stated that by the end of September, NCI will have amended the toxicity protocol in-house and will send it to FDA the first of October.

An NCI representative stated that as a topic of a future meeting, NCI would like to discuss what tissues in mice and dogs need to be done. Dr. Chabner questioned why the myeloid/erythroid ratio is required since it is expensive and rarely needed. Dr. Richman responded that it was probably originally included, like the monkey was, as an NCI proposal rather than a FDA proposal and FDA will not object if it is dropped.

Dr. Crout closed the discussion by stating that histopath is not required to be submitted until just prior to Phase II, but when it is available it must be submitted.

2. Monitoring of Clinical Trials

Dr. Hoth asked when FDA will be publishing the final regulations on monitoring of sponsors and monitors, and investigators. Dr. Crout replied that we do not know when this will occur. NCI estimates that they have 1300 protocols at 1000 institutions. If they must monitor them all even once every 3 years it will cost 2-3 million dollars out of a $30 million budget. One suggestion they have is internal monitoring by the oncology groups with NCI monitoring of the monitors. Dr. Crout explained that the regulations only require intensive on-site monitoring of the adequate and well-controlled studies on which the new drug application approval is to be based. Therefore, it is important to identify early the pertinent studies. Dr. Finkel suggested a separate meeting between NCI and HFD-180 to discuss exactly what kind of monitoring need be involved.

3. Accountability for Drug Distribution

There was a discussion in which FDA and NCI agreed that education of investigators is required, i.e., treatment of patients by protocol, maintenance of a patient log by the hospital pharmacy and strict record keeping which will be monitored at site visits. NCI pointed out that they receive about 1000 orders/month for investigational drugs which adds up to over a million doses per year.

4. Reporting of Adverse Reactions

Dr. Hoth reported that he has a rough draft of a new guideline to replace the current, tortuous flow chart for ADR reporting. Severe, life-threatening, fatal, alarming ADRs will require a telephone call to the monitor within 24 hours and a follow-up report to NCI within two weeks. NCI will evaluate the information and if they find a correlation between the investigational drug and the reaction, they will notify both FDA and the investigators.

Dr. Crout suggested that NCI meet separately with Dr. Judith Jones and her drug monitoring staff about what types of reactions should be reported immediately. Dr. Hoth replied that NCI needed guidance on reporting the "gray area" of side effects that are seen during Phases II and III. NCI would like guidance as to when it is necessary to report. Dr. Finkel defined severe reactions as those that would stop a study or modify the dosage. She also stressed that severe, life-threatening reactions are to be reported immediately even if it is an expected reaction. Dr. Crout emphasized that when many institutions are studying the same drug, it is important for the FDA to be able to act as the focal point of knowledge about that drug.

5. IRB Approval for Group C Drugs and Special Exceptions

Drs. Hoth and Crout brought out that when a patient is treated with a Group C drug by a physician no IRB approval is required; however, the informed patient consent must be obtained. Dr. Hoth asked for clarification in regard to special exceptions, that is, NCI grants about 50-60/month. Would emergency use with a follow-up review be sufficient? Dr. Crout deferred the question to Dr. Kelsey's staff, suggesting that there be a separate meeting between NCI and Scientific Investigations. Dr. Finkel requested that NCI submit a letter to Dr. Kelsey requesting clarification on this point.

Dr. Schepartz brought up the fact that NCI is spending large sums to support the Group C program. He asked whether the requests could be made directly to the manufacturer and would this require the manufacturer to monitor the drug administration? FDA stated that the drugs would remain in the Group C classification if distributed by the manufacturer and that the manufacturer would not be required to monitor the program.

6. IND 18,905 - Tricyclic Nucleotide

Two questions were raised: (1) FDA requested GLP certifications in its deficiency letter. The studies were done in 1979 before the GLPs were finalized. Would a conforming statement satisfy FDA? Yes. (2) Dr. Richman requested clarification of the new toxicology guidelines as to what exactly would trigger a special study.

Lee W. Ripper

cc:
Attendees (10)
HFD-150/Oncology File
HFD-150/LRipper:10/21/81
R/D Init.:WJGyarfas:10/23/81
F/T:jb:10/23/81:Wang #5669A(17)

Dr. HOTH. So I would say from my perspective, although relatively new at NCI, that we have had very productive discussions with them over the last—well, certainly, in my tenure there—and I think the record demonstrates that we have been working very hard with them in a number of areas.

In the adverse drug area, for instance, in addition to Dr. Kelsey's group, at Dr. Crout's suggestion, we met with Dr. Jones, who is the Director of the Division of Drug Experience, who is their particular expert in the area of adverse drug reactions. I think it is important to understand that adverse drug reactions is not a simple matter. I think perhaps all of us here today may have this idea that an adverse drug reaction is simply something that happens to a patient, and it is immediately obvious. In fact, in patients with advanced cancer, with many, many medical events going on, many of which may be due to their cancer rather than the drug, it is often impossible to distinguish between an effect due to the drug and that due to the disease. So that those of us who are on the front line, both at NCI and out in the field, are constantly faced with this difficult decision of exactly what event is caused by the drug and what has been caused by the disease.

In essence, to summarize, what we have done with our system is to say; "Let us increase the threshold of suspicion," so that we will report events that happen to patients even when there is even a likelihood, a small chance that it may be related to the drug. But I am trying to point out that there are ranges of certainty, and that we are trying to change that threshold.

Point 2, we will immediately communicate that to the FDA. And I can point to the fact that, in 1981, we have over 45 cases of adverse drug reactions that have been called or written to FDA immediately.

Senator HAWKINS. How many did you have in 1980?

Dr. HOTH. Probably about five.

Senator HAWKINS. Five in 1980?

Dr. HOTH. Approximately. I will have to get that for you.

[Information supplied for the record follows:]

ADVERSE DRUG REACTION REPORT

Date	Drug		Comments
April 1980			
9	Chlorozotocin	(NSC 178248)	2 pts with pulmonary interstitial disease.
August 1980			
11	VP-16	(NSC 141540)	Case report of a patient who died suddenly after IV VP-16. Happened in the Netherlands. Not on NCI sponsored study nor was drug supplied by NCI.
October 1980			
24	Piperazinedione	(NSC 135758)	Annual Report included 8 cases of toxicity.
December 1980			
4	Triazinate Not reported to FDA	(NSC 139105)	1 pt developed shaking chills after drug administration, WBC dropped to 2300 after 24 hrs. and to 500 after 48 hrs.
30	THC	(NSC 134454)	1 pt. with seizure following THC. No evidence that report was submitted to FDA.
February 1981			
18	Levonantradol	(NSC 331615)	Hypotension in 16 patients.
18	Chlorozotocin	(NSC 178248)	1 pt with renal failure.
March 1981			
6	Chlorozotocin	(NSC 178248)	Annual Report dealt with 1 pt with renal toxicity and 2 pts with chronic interstitial pneumonitis.
23	Azacytidine	(NSC 102816)	Annual Report included 1 pt with CNS Rxn and 1 pt with lethargy.

Date	Drug	Comments
March 1981		
25	Methyl CCNU (NSC 95441)	Possible adverse effect. Acute leukemia developed after treatment.
30	Ara-A (NSC 404241)	1 possible drug-related fatality with Ara-A at a dose of 1 mg//kg/day x 3.
April 1981		
11	Yoshi-864 (NSC 102627)	ADR submitted with the annual report.
	(June 17, 1981 - Sent Autopsy report to FDA)	
May 1981		
5	Indicine-N-Oxide (NSC 132319)	Telephone call to FDA concerning possible drug-related fatalities.
June 1981		
17	Mitoxantrone (NSC 301739)	4 pts with CHF
19	Bisantrene HCL (NSC 337766)	1 pt hypotensive
July 1981		
13	Indicine-N-Oxide (NSC 132319)	Written report of hepatotoxicity cases
15	Mitoxantrone (NSC 301739)	1 pt with tachycardia and shortness of breath. 1 pt with CHF. 1 pt with cardiopulmonary syndrome. 1 pt with atrial fibrillation.
28	WR-2721 (NSC 296961)	3 pts. febrile and hypotensive. No evidence report was submitted to FDA.
August 1981		
6	Mitoxantrone (NSC 301739)	Cardiotoxicity: 1 new pt Followup on pts 1,5,6,8.
11	Zinostatin (NSC 157365)	1 pt experienced a flushing Rxn with increased shortness of breath and tachycardia.

Date	Drug	Comments
August 1981		
12	Mitoxantrone (NSC 301739)	Cardiotoxicity: Dr. Vietti's call
21	Chlorozotocin (NSC 178248) DOR - March 20, 1981	Nephrotoxicity: 1 Pt - Dr. L. Baker
21	PALA (NSC 224131) DOR - July 1981	Septic and died: 1 pt - Dr. F. Camacho
25	Mitoxantrone (NSC 301739)	Cardiotoxicity: 3 pts - Dr. Vietti 1 pt - Dr. Luedke Necrosis: 1 pt - Dr. Murray
26	VP-16 (NSC 141540)	1 pt with myositis and arthritis (swelling and pain) in both shoulders, the right arm and forearm and left knee.
September 1981		
3	Mitoxantrone (NSC 301739)	Cardiotoxicity: 1 pt - Dr. D. Alberts Followup - pts 7,2, & 3
4	Bisantrene HCL (NSC 337766) DOR - August 21, 1981	Hyperglycemia: 1 pt - Dr. N. Kemeny Cardiac Arrhythmia: 1 pt - Dr. N. Kemeny
4	AT-125 (NSC 163501) DOR - August 24, 1981	3 pts experienced episodes of diaphoresis with vasoconstriction
4	High Dose Methotrexate (NSC 740) DOR - January 22, 1981	1 pt suffered a fatal pulmonary edema.
8	Mitoxantrone (NSC 301739)	Cardiotoxicity: 1 pt - Georgetown
8	Chlorozotocin (NSC 178248) DOR - August 9, 1981	Interstitial pneumonitis: 1 pt - Dr. J. Goedert
11	Mitoxantrone (NSC 301739)	Cardiotoxicity: 1 pt Dr. Vietti Tabular Summary - 12 pts Followup - pts 7 & 12

Date	Drug	Comments
September 1981		
18	Mitoxantrone (NSC 301739)	Table from Dr. Von Hoff SWOG studies
22	Mitoxantrone (NSC 301739)	Cardiotoxicity: 1 pt - Dr. A. Denes
23	VP-16 (NSC 141540)	Pneumonia: 2 pts - Dr. J. Bennett
23	Mitoxantrone (NSC 301739)	Cardiotoxicity: 1 Pt. Dr. Yap
30	Mitoxantrone (NSC 301739)	Cardiotoxicity: Cyanimid - Pts 7, 18, 19, 20, 21, 22, 23 Dr. Vietti - Pt 7
30	Mitoxantrone (NSC 301739)	Cardiotoxicity: Pt 24 - Dr. P. Mahal
Oct. 1981		
5	Mitoxantrone (NSC 301739)	Renal Failure: 1 Pt - Dr. L. Einhorn Cardiotoxicity: Followup - Pt. 14
5	Dichloromethotrexate (NSC 29630)	Pleural effusion Pulmonary edema: 1 Pt - Dr. J. Blom
6	Mitoxantrone (NSC 301739)	Cardiotoxicity: SWOG: followup Pt. #20 2 new Pts. - #25, #26
6	VP-16 (NSC 141540)	AMML & Death: Dr. D. Jackson 55 yom - oat cell ca developed AL & Died
7	Mitoxantrone (NSC 301739)	Cardiotoxicity: Followup - Pt. #23

Senator HAWKINS. That is a lot of action this year.

Dr. Bono, you were Chief of the Investigational Drug Branch from 1977 to the beginning of this year, which would be 1981; is that right?

Dr. BONO. Yes; that is correct.

Senator HAWKINS. Am I correct in saying that as Chief of that Branch, you were responsible for the monitoring of clinical trials and the reporting of adverse drug reactions to the FDA and to the NCI-sponsored clinical investigators?

Dr. BONO. I was a comonitor for each of the IND applications that we have on file with the FDA.

Senator HAWKINS. So you were coresponsible?

Dr. BONO. Coresponsible with members of my staff, the drug monitors.

Senator HAWKINS. Were you here for Dr. Hensley's testimony earlier, concerning his inspection on the NCI's handling of methyl-CCNU adverse drug reactions?

Dr. BONO. Yes.

Senator HAWKINS. My question to you is, Why were the reports received by your office in 1978 not forwarded immediately, as Dr. Hoth has said they are now going to do? Why were they not forwarded immediately to the FDA, and more importantly, why was this information not forwarded to all of NCI's clinical investigators?

Dr. BONO. The reason that the initial reports to us from the group in New York in spring and summer of 1978 and then again from Boston in the fall of 1978 is that, as we received this information, what we received was a suggestion and a hypothesis that the renal toxicities seen in these people were associated and caused by methyl-CCNU. What we proceeded to do was to investigate these reports and to expand our data base so that we would be in a position to make some statements about the conclusions to be drawn from these suggestions. And in fact, in January 1979, our studies had proceeded to the point where we felt that this was a reliable observation and that for certain patients who had received certain dosages of methyl-CCNU for certain periods of time, that there was indeed a risk of developing renal toxicity. And at that time, we notified all investigators who were continuing their investigations with methyl-CCNU, and we also notified the FDA of our findings and our actions.

Senator HAWKINS. What date was that?

Dr. BONO. That was in February of 1979.

Senator HAWKINS. Why were the 1978 reports of kidney failure in patients not provided to Dr. Hensley when he first inspected the NCI concerning this matter in 1979?

Dr. BONO. I am puzzled by Dr. Hensley's report to the committee this morning, because the data that he is referring to was included in our report to FDA in 1979, in February. In fact, that is the information upon which we were basing our conclusions.

Senator HAWKINS. I have a memo here dated July 11, 1979, from you to the Director of the Division of Cancer Treatment, in which you discuss the FDA's request to inspect the NCI's handling of methyl-CCNU. Your memo states, quote: "It seems to be unnecessary to conduct this exercise once again," and then you further state, "I am of the opinion that we should not comply with this request and that this issue be brought to the attention of Dr. Finkel or Dr. Crout of FDA."

Do you have a copy of that letter?[2]

Dr. BONO. Yes.

Senator HAWKINS. Why did you write this memo, and why were you opposed to the FDA inspection of methyl-CCNU?

Dr. BONO. The reason I wrote that memo, as Dr. Hensley mentioned, when they approached my office for a meeting, it was at the level of a general inspection and discussion of the way in which we develop a drug, and in this case, methyl-CCNU.

My concern was that all members of the FDA were not fully aware of the rather lengthy planning, discussions, and presentations of the way in which we proceed with the development of our drugs, which took place during the year 1977 and resulted in the document which is included in our drug master file. So I felt at that point, what we would likely have to do would be to meet with members of the FDA staff and once again go through the process of discussing the ways in which we monitor our clinical trials, select our investigators' and do our reporting.

And following that memo, the agreement was that the existence of the drug master file be brought to the attention of the investigators and that they study it prior to coming to meet with us.

Senator HAWKINS. I have another one of your memos. This one is dated April 30 and directed to Dr. Macdonald, and this subject says, "Lack of compliance with FDA regulations and the misuse of NCI investigational agents." Can you tell us what prompted you to write this memo?[3]

Dr. BONO. Yes; I can. This was in the spring of 1980, just following the annual spring meetings of the American Association for Cancer Research and the American Society for Clinical Oncology, at which all of the significant clinical studies during the previous year are reported. And at that meeting, a number of studies were reported, which our drug monitors became aware of, that were not on record in our Branch as having been submitted to us for sponsorship to the Food and Drug Administration.

This represented and presented to me and the program two problems—one, a clear lack of compliance with a regulation that there has never been any doubt about, and that is that we will review and submit to FDA protocols that are approved for the study of investigational agents, and the second problem that it presented is that we were at a point in the development of our drug development plan where such studies represented a lack of compliance with NCI's plans for the development of drugs. I would like to explain that a little bit.

As part of the drug master file document which we submitted and was accepted by FDA in 1978 was the classification of our drugs into various groupings which we have labeled groups A, B, and C. These groups characterize the status of a drug in its development. It characterizes the extent of information we have about the drug, and also, the implications about the approaches and strategies that are going to be taken for the further evaluation of the usefulness of these drugs.

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[2] Memo dated July 11, 1979, from Bono to the Director, OCT, may be found on p. 4.

[3] Memo dated Apr. 30, 1980, from Bono to Associate Director, CTEP, may be found on p. 85.

Now, AMSA at that time was classified as a group A drug, and one of the conditions of a group A drug is that we are attempting to identify its single-agent activity and efficacy in any one of a number of human tumors, and that at that point, it is not appropriate for combining that drug with another drug in a clinical trial. So that, in addition to these being out of compliance with FDA, they were also out of compliance with our own plans for the development of these drugs.

Senator HAWKINS. In this memo, you ask Dr. Macdonald, your superior, for his "permission" and "assistance" in making it widely known that the use of NCI's drugs in clinical studies not approved by NCI "will result in serious action by NCI." You go on to state that you are aware of several such unapproved studies at two cancer centers, and that there are many others like this. And you further state:

> I believe that I cannot ask our NCI staff to do the jobs of both meeting FDA regulations and of ensuring the safe and coordinated development of our new drugs, while allowing this misuse of investigational agents to continue.

Was there any response to your memo, and if so, what action was taken?

Dr. BONO. Yes. I have thought back to this, and I know that I did not get a written response to this memo. In fact, I cannot explicitly remember a discussion with Dr. Macdonald about this. But I know from my own policies and procedures that I concluded that the approach that we had previously been taking, that is, to gain the cooperation of our investigators by education and persuasion, rather than by applying threats of adverse action, was our prior policy. And at this point, I was feeling——

Senator HAWKINS. You were not upset, then, about not getting an answer?

Dr. BONO. I felt that—no; the answer was that I should continue on with the policy of persuasion and education, rather than to go to a policy of threat.

Senator HAWKINS. Rather than send a letter?

Dr. BONO. Yes.

Senator HAWKINS. Dr. Macdonald, why didn't you respond in writing to Dr. Bono's memo?

Dr. MACDONALD. I talked to him. Basically, it was a policy decision that Dr. Bono was presenting me with, for my decision, actually, with these studies as examples. And what he wanted to know was basically, how hard to come down on people doing this kind of research.

Now, the first thing I did was to look at the studies that were done, and it turns out that those studies had been all published, had all been completed—there were a total of, I guess, 46 patients, 10 of whom had responded, 2 of whom had complete regression of their tumors.

I was interested, actually, in Dr. Hensley's comments this morning about what he considers therapeutic research, the fact that the patients had benefited from this relatively innovative use or combination of drugs, in cancer treatment. Many of our investigators are quick to do that, to want to innovate. I did not want to cut that off.

But I also felt strongly that we could not condone any breaking of the regulations.

So what I suggested to Dr. Bono was that the drug monitors in their daily and their weekly conversations with investigators, remind them that this is not to be done, that this be mentioned at a phase I, phase II meeting that this is not to be done. I did not say send a letter; I did not offer to send a letter myself. I think that it is interesting to——

Senator **Hawkins**. When were those meetings held?

Dr. **Macdonald**. The meetings were held in October and July 1980. I might add that this was brought to my attention as the first example in my tenure as the Associate Director of this sort of thing going on. When further information was brought to me, which was about a year later, the study with ara-A and DCF and then the study with the homofolate analog at M. D. Anderson, I think that, as you have seen, action was taken on a much firmer basis. Dr. Hoth confiscated the drug from the M. D. Anderson Hospital; he removed the permission to do clinical trials from the principal investigator. He required that all the protocols that were being done be reviewed. And of course, the other affair with the homofolate resulted in a site visit to the M. D. Anderson Hospital, which resulted in the loss of the contract under which the study was being done.

Senator **Hawkins**. As you look back on this whole episode, what action do you think you should have taken as a result of the written memo?

Dr. **Macdonald**. I think that what it did was raise my sensitivity to the issue. I think that my response to the ara-A/DCF study that was reported to us the same way, through a publication, actually, in 1981, resulted from the fact that that study was done not on a protocol we did not know about. It was done on a protocol that had been submitted to us and disapproved, and disapproved for reasons of patient safety, and that is a totally unacceptable problem, and that is why we came down hard on that issue.

Senator **Hawkins**. Dr. Marsoni, you were a drug monitor and worked under Dr. Bono at the time of his memo of April 30, 1980, were you not?

Dr. **Marsoni**. Yes.

Senator **Hawkins**. Were you aware of the memo when it was issued?

Dr. **Marsoni**. I must admit that I do not recall exactly this memo. I recall the situation happening at that time, and the fact that Dr. Bono was with me, with the other monitor in the Branch, and has always pointed out that the investigator has to follow the rules that are agreed upon between the NCI and the FDA that are contained in the master drug file, and among these rules is that no protocol should be initiated in a single institution without NCI approval.

Senator **Hawkins**. Do you recall any special instructions in connection with Dr. Bono?

Dr. **Marsoni**. Every drug monitor that comes and works for us is specially instructed about this. I mean, it is the law under which we operate all the time. And I think——

Senator **Hawkins**. Were they in writing, or do you all just have discussions daily?

Dr. **Marsoni**. Well, there are several operational plan books that are given to the drug monitors as soon as they come onboard, and the drug master file is available, and in both, there is an explanation not only of what the regulations are, but how we should comply with them.

Senator **Hawkins**. What action do you feel now, in hindsight, you should have taken in response to this memo?

Dr. **Marsoni**. I think that because of what exactly Dr. Macdonald said a few minutes ago, probably that was the right decision, and that really raised everybody's consciousness about the possibility of this episode happening again. And a proof of that is that this year, while I was drug monitor of the DCF drug, I raised the question of the DCF/ara-A study, and immediate action was taken.

I think I would like to underline the difference between the two occasions. In the first case, the drug involved was a very active drug, and at that time, was a drug active even in breast cancer, and I think that what the investigator involved tried to do was to combine this experimentally active drug with other drugs in order to enhance the activity of both drugs. And actually, they succeeded; there was a 22 percent response rate in the breast study with this particular drug.

So, they were really doing the therapeutic research that Dr. Hoth was referring to before and for which he was hoping that regulation too tight will not strangle.

Senator **Hawkins**. Dr. Hoth, could you give us your best recollection as to what happened after Dr. Bono's memo was issued?

Dr. **Hoth**. Yes. Well, I think, as I said, there were discussions internally. Another factor we considered at that time was that at both of the institutions in question, we had just brought into place a monitoring contract that we referred to as our Clinical Trials Monitoring Service, and we felt that we should give that contractor an opportunity, since they were at the very beginning of their efforts at that time. In other words, we thought that we were bringing into place mechanisms that would deal with that. I think the other key thing is that when we saw this happening again, we took action on it.

Senator **Hawkins**. You heard the earlier testimony of Dr. Hensley on his review of DHAD filings. Can you explain why only 2 of the 33 protocols for this drug gave a clear warning of toxicity to the heart?

Dr. **Hoth**. Yes. I think that entire area should be put into perspective, and if I could have a moment or two to describe our view on the issue of heart damage from Mitoxantrone.

The initial animal studies that were part of the IND which NCI filed included a detailed study of the effects of this drug on the hearts of dogs and showed no effect. A second study conducted at Ohio State University for NCI to which Dr. Hensley referred to in his testimony about which he stated that it demonstrated dogs dying within hours, in fact, showed that the dogs had low blood pressure, and they died of what we medically refer to as hypotension. The scientists who did that study in their written conclusion felt that there was no evidence that the heart itself was affected by the drug. There are many other mechanisms, many other causes, for low blood pressure. There was no evidence from that data at that time, from either the Ohio State study or from the dog study, that this drug caused heart damage.

Now, there was a separate study, which was conducted in rabbits, and that study did show heart damage. And unfortunately, due to an internal administrative lapse, that study did not reach my attention until June of this year, when Dr. Turner of the FDA pointed that out to me.

I think, however, that that would not change the way that we would pursue this drug. Now, let me back up. What are we talking about? What is the magnitude of the effects that we are referring to?

No. 1, we are talking about a cancer drug that is helping patients, and it is helping patients in excess of any potential damage. We have substantial evidence of activity in both leukemia and in breast cancer, and there have been hints of activity in lymphomas, head and neck cancer, Hodgkin's disease, Ewing's sarcoma, neuroblastoma, and prostate cancer. So we think this is an exciting drug; it offers promise in the treatment of cancer patients.

In regard to the specific issue of cardiotoxicity, of heart damage, we have on file 16 cases of heart failure among the patients taking this drug, and of those, 5 patients have died. Now, in every single case, all 16 of those patients with heart damage, there are other factors which are known to cause heart damage in that patient's history. The principal factor was that 14 of those 16 patients received a drug called Adriamycin before they ever were treated with the experimental drug. Adriamycin is one of the most active cancer drugs there is, and this drug is known to cause damage to the heart. Nevertheless, in spite of that, we use it——.

Senator **Hawkins**. Let me interrupt you at this moment. We have a few minutes to go and vote, so we will have a short recess.

[Short recess.]

Senator **Hawkins**. Back on the record—and for the record, they say that is the last vote today, but we will see.

Dr. Hoth, you were talking about the promising effects of the drug, DHAD. What about the letter from the FDA, addressed to you and dated October 26, 1981? The letter refers to the NCI's use of DHAD and states that the only phase II clinical study results reported show one complete response in over 500 patients treated with DHAD, The letter points out that in the last 4 months, over 20 cases of congestive heart failure in patients who have received DHAD have been reported. Then the letter goes on to suggest that NCI question the continued use of this drug.

[The letter referred to follows:]

IND 16,802

National Cancer Institute
Attention: Daniel F. Hoth, M.D.
Chief, Investigational Drug Branch
Cancer Therapy Evaluation Program
National Institutes of Health
Bethesda, Maryland 20205

OCT 26 1981

Dear Dr. Hoth:

Reference is made to your Notice of Claimed Investigational Exemption for a New Drug (IND) for Mitoxantrone (dihydroxyanthracenedione; NSC 301739; DHAD).

In the last four months, over 20 cases of congestive heart failure in patients who have received DHAD have been reported to this Administration. However, the only Phase II clinical study results reported to us in writing to date are from the Southwest Oncology Group showing one complete response in over 500 patients treated. In light of this seemingly unfavorable risk/benefit ratio, we feel that at this time you should develop and submit a comprehensive plan for future studies, if any, on this drug. This submission should act as an interim progress report and include the total number of patients entered into study to date, tumor response rate with each dose schedule and tumor type, a list (with descriptive titles) of all studies with a note as to which are still open, and information on toxicity, i.e., which were the most frequently seen toxicities and in what percentage of the patients did they occur.

This request is also being made to Lederle Laboratories.

Your prompt written reply will be appreciated so that we may continue our evaluation of your IND. We remind you that the interstate distribution of this drug for investigational use is subject to the Federal Food, Drug, and Cosmetic Act and the new drug regulations and may be terminated under the conditions stated in section 312.1(d) of the regulations.

Sincerely yours,

William J. Gyarfas, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Bureau of Drugs

cc:
IND 16,802
HFD-150
HFD-150/DOC.
HFD-160/MHansley
HFD-150/CSO/LRipper:10/15/81

R/D Init.:RGScully:10/15/81
JRJohnson:10/15/81
HLWalker:10/16/81
WJGyarfas:10/17/81
F/T:jb:10/20/81:Wang #5635A(17)

INFORMATION REQUEST

Senator **Hawkins**. Has the NCI responded to this letter, and if not, are you giving some thought to the FDA's suggestion?

Dr. **Hoth**. I would be delighted to answer that. I am glad you asked about that letter. I received that yesterday. I think on both sides of Rockville Pike, we have bureaucracies involving our mailrooms, although the letter was dated October 26——.

Senator **Hawkins**. Maybe since it is 20 cents, you will get it faster.

Dr. **Hoth**. That is right. We were lined up, waiting to buy 2-cent stamps, actually. [Laughter.]

The one area that I would like to point out that is a bit of concern to us at NCI is that part of our master plan says that we will supply FDA with copies of minutes of all of our major meetings held at NCI to review drug status. And one of those meetings was held in June of this year, and we did, in fact, have a very large amount of data about this particular drug that was included in those minutes, and I checked with my staff, and they did in fact mail that to FDA.

So I think that they do have a little more data than is indicated here. However, in general, we are going to be delighted to reply to that, and we will give them a summary of what I have told you here this morning, which is, just to recap, that we think that this drug has exciting activity in leukemia and in breast cancer; that overall, more than 1,200 patients have received Mitoxantrone, and yet, as of now, we have 16 cases of congestive heart failure; 5 patients have died with congestive heart failure, and in not a single case can we be sure that Mitoxantrone, was the cause, and in fact, we think that the scientists who look at this feel that it is very much of an issue still as to whether this drug causes cardiac damage.

Nevertheless, we have undertaken three new studies to look at that. A year ago, we started a study at Ohio State to compare the possible heart effects of this drug with Adriamycin, a standard drug, and we have two new studies that are specifically evaluating this problem. So we are moving in that area, in summary.

Senator **Hawkins**. I note with interest your memo of August 3, 1981, to the Acting Director of the Division of Cancer Treatment, in which you recognize the need for, and the purpose of, an improved monitoring system. In your memo, you state that such a system "will ensure detection of systematic, intentional inaccuracies in the material submitted to the NCI, as well as the occasional inadvertent error." Your memo further states that "site visits should also verify adherence to the procedures required for the accountability of drug distribution, requirements for obtaining informed consent and evaluation of completeness of reporting of adverse drug reactions." I like the sound of that, but can you tell us if and when such a system will be established?

[The memo referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date August 3, 1981

From Chief, IDB, CTEP, DCT

Subject Future Prospects for Clinical Trials Monitoring

To Acting Director, DCT, NCI

Over the last two months there has been considerable discussion regarding the issue of NCI monitoring of all sponsored clinical trials. There has been much discussion here in the CTEP on this topic, and the purpose of this memorandum is to outline this problem in broad strokes. It should be pointed out that any system to be implemented may be significantly shaped by the new proposed FDA regulations to be released within the next one to two months. Examination of an unofficial rough draft of these regulations outlines in detail for the first time the responsiblities of the IND sponsor for monitoring sponsored clinical trials and accounting for drug use. These proposed regulations are considerably more stringent than those currently in effect, and include the requirement for an annual on-site visit of all institutions utilzing investigational agents by a monitor designated by the IND sponsor. The purpose is examination of subject records in an attempt to ascertain accuracy of reporting and adherence to approve protocols. An additional aspect to the new proposed regulations include accountability for distribution and usage of experimental agents as well as reclamation of unused material.

It is clear that any clinical trials monitoring program organized by us at this time should be designed to meet requirements of studies utilizing investigational agents since those will be operating at the most stringent requirements. It is also clear that, if the final version of these new regulations is similar to the draft which we have seen, the impact on the Investigational Drug Branch activities will be considerable. In fact, it seems clear to me that serious consideration should be given to renegotiation of the section of the NCI Drug Master File regarding operational plans for clinical trials, once we review these new regulations. There may be some way to standardize the impact of these new regulations on NCI in this way. These considerations aside we have been examining the issue of clinical trials monitoring from our own vantage point while realizing that finalization of any plan will depend to some extent on these new FDA regulations. The information below outlines the major issues and alternatives associated with this problem. Comments are designed to clarify the issues and lay the groundwork for more definitive discussions.

1. Objective of the Monitoring

We feel that the principal goal of the monitoring service should be to verify the accuracy of data submitted on clinical trials supported by NCI by means of periodic site visits. This should include studies utilizing investigational agents as well as all others. This will insure detection of systematic intentional inaccuracies in the materials submitted to NCI as well as the occasional inadvertent error. These site visits should also verify adherence to the procedures required for the accountability of drug distribution, requirements for obtaining informed consent and evaluation of completeness of reporting of adverse drug reactions. A system designed around these objectives would in all likelihood satisfy the majority of requirements in the new FDA regulations. It should be pointed out that the proposed regulations require that the sponsor (i.e. NCI) assure that the clinical investigators are meeting their responsibilities.

2. Methodology of the Monitoring Program

The magnitude of this project becomes somewhat clearer when we consider that there are approximately 260 cooperative group institutions most of whom have satellite institutions that should be site visited as well. Add to this estimate the approximately 100 institutions funded by contract and we can conservatively estimate that between 600 and 900 institutions would require site visiting at some interval. In discussions during the course of two months and in examination of the proposed new FDA regulations, the time interval being given the most consideration is one year. Thus we are talking about the conservative estimate of 600 to 900 site visits per year. An alternative proposal would include an adjustment on that one year interval based on the results of the individual institution's most recent site visit. Institutions with good site visit reports could be site visited at longer intervals. Institutions with unsatisfactory could be site visited in less than one year. Nonetheless, we are certainly talking about a a very large number of site visits. This impacts directly on the alternatives for the personnel to perform the site visit. The site visit teams should be made up of no less than one physician and one data manager equivalent.

The magnitude of this effort undoubtedly removes it from the realm of performance by NCI staff itself. One alternative currently being explored with the Cooperative Groups is a common program for self monitoring the Groups with site visits at all institutions on an annual basis. While this sounds superficially attractive, it will not be inexpensive and will still require some sort of overlaid monitoring process by NCI staff or contracted monitoring staff. I feel very strongly that we cannot leave the Cooperative Groups to monitor themselves without some supervision and cross-checking. Furthermore, since NCI will have to provide monitors for all other trials outside of the cooperative group framework, it probably will be more economical to do the entire job through one mechanism, as described below.

Another alternative to the above idea is the establishment of an independent clinical trials monitoring contractor who would perform all the monitoring site visits. The advantages to this idea are that the monitors and site visitors would be entirely impartial and that their fact finding would be less open to criticisms regarding bias. Furthermore, using a single entity to do all monitoring would assure equal treatment of all clinical investigators, would permit a closer and more clearly defined link between NCI staff and the monitoring professionals, and would allow NCI more flexibility and access in the critical start-up phase as these broad policies are implemented in detail.

However, this would be an expensive project, with preliminary estimates at $1-2 million per year. Economies of scale might apply, since even if the Cooperative Groups monitor themselves, NCI would have to visit many of these same institutions to review their non-Group trials. Therefore, one team could site visit all the departments of each of the institutions within a given geographic area at one time, in contrast to separate visits by each Group, often to institutions within the same geographic area. Furthermore, a full time professional staff (of a contractor) performing site visits probably would be more efficient and therefore less expensive per site visit.

In any case whichever of these options are chosen, an increase in the staff in the Investigational Drug Branch and the Clinical Investigations Branch will be required to supervise this operation and deal with the ultimate question of NCI reaction to unsatisfactory site visit reports.

3. Site Visit Process

We envision that institutional site visits to be scheduled in advance. Site visit teams should consist of one M.D. and one or two data managers. The site visitors will examine a random selection of charts with a short advance notification to the institution of the precise charts. The precise number to be reviewed will be set later, but a starting point might be 5 to 10 per cent of the institution's charts or 5 to 10 charts, whichever is greater, will be examined annually. Data will be compared between the patient's primary medical record and the case report forms submitted to the Cooperative Group's operations office in the case of a group or to NCI in the case of single institutions or contractors. The site visitors will examine information pertinent to adherance to the protocols as well as verify treatment response reported by examining x-rays, scans and other diagnostic studies. This may well include examination of criteria for eligibility, dates of surgical procedures, pathology reports, and treatment records pertinent to chemotherapy administration and radiotherapy. Additionally, informed consent for each patient chart shall be examined. Primary records would be screened for adverse drug reactions and later compared with reports received by NCI.

Also discussed as a probable function of these site visits is an examination of pharmacy records. This may integrate the monitoring program with any new IDB drug distribution and tracking policies. Pharmacy site visits could include review of records pertinent to receipts of drug shipments, dispensing of each drug and current inventory. Pharmacy procedures for handling investigational agents should also be examined. It is my understanding that this will be required by the new FDA

4. Site Visit Reports

At this time it seems appropriate that detailed standardized forms should be developed for use by the site visitor. We believe that the results of the site visit reports should be made available not only to NCI but to the investigator, institutions IRB, and the Cooperative Group Operations Office when appropriate. An appeals process should be established whereby an investigator can submit clarifying information after the site visit.

5. Final Comments

The establishment of a monitoring program with annual site visits is only half of the information loop. The second half includes feedback on the results of these site visits to the institutions and making this information available to the FDA when investigational agents are involved. Feedback to the institutions is another issue that must be carefully thought out. Most of these institutions will be funded with grants or contracts and be receiving investigational agents. A scale of measuring an institution's performance on the site visit must be developed with appropriate NCI measures and response. Whatever the details of this process, it must be carefully thought out and discussed in advance with both the Cooperative Group Chairmen and the DCT Board of Scientific Counselors.

While the above comments briefly outline the issues and sketch possibilities for a monitoring program, ths whole business should be regarded as a plan in evolution. We should not underestimate the impact of the new FDA regulation nor the possibility that the existing Master File may require some renegotiation.

This memorandum represents the initial thoughts of the senior staff of CTEP, following two lengthy meetings on the subject.

Daniel F. Hoth

Daniel F. Hoth, M.D.

cc: Dr. W. DeWys, Dr. J. Henney, Ms. K. Horgan, Dr. E. Jacobs,
Dr. D. Kisner, Dr. J. Macdonald, Dr. S. Schepartz, Ms. D. Tisevich

September 16, 1981

Chief, Investigational Drug Branch, CTEP

Proposal for Monitoring of Clinical Trials via Periodic Site Visits

Acting Director, Division of Cancer Treatment, NCI

The DCT recognizes an increasing requirement to assure the accuracy of data reported on research clinical trials supported by this Division. It is proposed that this will be accomplished by periodic site visits to each site of clinical investigation. The scope of research to be site visited includes clinical trials involving not only chemotherapy, but also immunotherapy, radiotherapy, or surgery, either alone or in combination of two or more modalities. In part, the impetus to undertake this effort comes from a set of regulations proposed by FDA. These were originally published in the Federal Register in 1977, and we are told by FDA that they expect them to be released this fall. The relevant section is excerpted on the following page.

Also attached is an outline of the key features of this project as we now envision it. This document will serve as an outline for a more detailed presentation at the October meeting of the Board of Scientific Counsellors.

Daniel F. Hoth, M.D.

Policy for Monitoring of Clinical Trials: Key Elements

This is the set of essential items for site visiting which should apply to all DCT sponsored clinical trials.

1) Periodic site visits shall be conducted for this primary purpose of validating the data submitted on research clinical trial. A second purpose is to review the procedures for handling of IND drugs.

2) Site visits will be made to each institution entering patients on research protocols sponsored and/or funded by NCI. Those sites functioning as satellites of principal institutions will also be site visited.

3) Selection of institutions for site visits will be random, but such that each will be visited every three years. Every institution will be at risk at all times, but the probability will vary with the time since the last visit.

4) The team conducting the visit should be composed of qualified individuals, one of whom should be competent to interpret medical information such as patient histories, physical examinations, x-rays, etc. In general, it is expected that this should include a physician.

5) Site visit teams should inspect:
   - Source data, i.e. the primary record which documents the validity of the submitted data.

- Source data to be reviewed will include 1) information which verifies patient eligibility for particular protocol i.e. pathology reports, surgery reports, date of birth, etc.

2) Patient data: records of protocol treatments, physical examination, laboratory data, x-rays, radionucleotide and CAT scans, etc.

- Records of disposition of shipments of investigational agents. Investigators shall maintain records of the identification of each subject receiving the drug, and the protocol under which the patient is treated. Patients will be selected at random from these drug distribution lists to verify that patients receiving IND drug were entered on the stated research protocol.

- Copies of informed consent.

6) Site visits will be conducted with minimum advance notice to the institutions.

7) Representatives of the NCI may attend any site visit without prior notice.

8) Reports of results of site visits should be provided to Group Chairman, investigator, institution IRB, and NCI.

9) Appropriate procedures for resolving discrepancies will be developed. In general a graduated series of steps ranging from written clarification to early repeat site visits to formal NCI review, and finally, in severe cases, an NIH investigative review.

EXCEPTED FROM PROPOSED REGULATIONS ENTITLED "OBLIGATIONS OF SPONSORS AND MONITORS OF CLINICAL TRIALS", PUBLISHED IN THE FEDERAL REGISTER IN SEPTEMBER, 1977

"b. Periodic visits

The monitor shall maintain personal contact with each investigator by visiting the investigator at the site of the investigation during the investigation... to assure that the following obligations of the investigator are being fulfilled:

I. Continued acceptability of the facilities.
II. Adherence to the protocol or investigational plan and applicable Food and Drug Administration regulations regarding obligations of the investigator.
III. Maintenance of adequate records of subject identification, clinical observations, laboratory tests, and drug receipt and disposition.
IV. Reports submitted by the investigator in support of the safety and/or effectiveness of the test article are timely, adequate and accurate.

2. These periodic visits shall include a review of the source documents relevant and necessary to making the determinations described in paragraph (b)(I) of this section (e.g. subject records and case reports) for accuracy and completeness of information, illegible entries, missing data including omission of specific individual data elements and any concomitant drugs and intercurrent illness, and missing subject visits or examinations. To do this, a comparison of a representative number of case reports with the investigator's individual subject office records is necessary. In addition, the monitor shall document those subjects lost to the study and the reasons for such dropouts. Where associates of the investigator prepare the case reports, the monitor shall assure that the investigator himself not only reviews these case reports but also determines the accuracy of these reports and their compatibility with source documents.

3. The frequency of the periodic visits shall be sufficient to assure that the obligations of the investigator are being fulfilled. If the time interval between visits will be greater than 12 months, the monitor shall state in the records the reason for the longer interval."

Underlines added for emphasis.

Dr. HOTH. Yes, absolutely. I will be meeting on Thursday with the contractor who performs our phase I monitoring, and I would like to just point out to you, I had brought down here, flown down from New Jersey this morning, the latest printout. This, what you see in front of you, is all of the data that we receive every month at NCI on our phase I trials. This same group, which we refer to as our clinical trials monitoring service, makes site visits to our phase I contractors, and they do that now three times per year.

Now, we are meeting with them this week to expand their efforts to monitor our other contract groups—that is, groups which do clinical trials, phase II and phase III, the more advanced clinical trials. We will be expanding in that area very rapidly.

The other thing I would like to point out is that we have another major group of clinical researchers who receive moneys from NCI. We refer to those as our cooperative groups, our clinical cooperative groups, and several of those groups have, for a number of years, had teams of their investigators who go out and make site visits and actually do this very kind of work. So we feel that there has been an evolution in this area, and we are going to continue. We have met with the chairmen of all our groups in August and asked them to develop plans to further conduct these site visit monitoring activities.

Senator HAWKINS. One final question for you, Doctor. Do you intend to make an effort to identify all of the clinical investigators who participate in the conduct of NCI-sponsored clinical trials? There was testimony earlier that your agency does not know who they all are.

Dr. HOTH. Yes. We think that what we face here is an educational process, that is, that some investigators may not understand their responsibilities in this area, and we have in the last week mailed a request out to all of our investigators, requesting that they register with us, all of our cooperative groups which have large operations offices, which have the capacity to do this—we will be identifying every investigator that is associated with us and getting that into our list, which will be forwarded to FDA. I have had conversations with Dr. Gyarfas, who is the director of that division—Divison of Oncology and Radiopharmaceutcials—on this matter, and we will be happy to continue to discuss that with them.

Senator HAWKINS. You have had a lot of activity this year, have you not?

Dr. HOTH. Well, I think that that may be an impression. The questions that you have asked me, of course, are current problems. What we are not looking at are the problems that existed in 1974 and 1975. During those years there were many very important things that went on during that time. The drug distribution system went from virtually handing out drugs to any investigator that wanted them, to a very tight classification. We developed a drug master file, a memorandum of understanding, with the FDA. The screening system, the way we identify promising new drugs in animals, was completely redesigned during that time period. Our toxicology program was redesigned. There has been enormous activity, and misimpression may be created.

Senator HAWKINS. And your chart has been redesigned.

Dr. **Hoth**. That has been changed, yes.

Senator **Hawkins**. Mr. Davignon, I understand you run NCI's drugstore; is that correct?

Mr. **Davignon**. Yes, you might call it a drugstore in a very broad sense——

Senator **Hawkins**. I am just a layperson.

Mr. **Davignon**. I am responsible for the development of the drug products for human trial.

Senator **Hawkins**. How long have you had that position?

Mr. **Davignon**. I have been with the Cancer Institute since 1963, and I have been Chief of the Pharmaceutical Resources Branch, my present position, since about 1976.

Senator **Hawkins**. Could you give us some estimates on the expansion of the NCI's drug distribution over the past 5 years and how much it has cost?

Mr. **Davignon**. Are you speaking of the drug costs or speaking of administrative efforts?

Senator **Hawkins**. Drug costs.

Mr. **Davignon**. We purchase approximately $4 to $4.5 million a year, for drug supplies, and commercially available products. In the last year, we have reduced our distribution of commercial drugs.

Our other effort has been through a contract program where we develop investigational drugs, and that—including our chemical procurement activities—involves about a $5.5 million annual effort. This represents a distribution of about 800,000 injectible units a year, and several thousand oral products. That is individual tablets.

Senator **Hawkins**. Do you have a percentage of what the increase would be over the last 5 years, if that is your current distribution and current purchases?

Mr. **Davignon**. The increase has not been significant financially in our contract program. We have worked on a level budget for several years prior to this, and last year we had a slight increase, and this year, we anticipate a slight decrease.

My particular program, the expenditures are based on the needs of the clinical trials.

Senator **Hawkins**. Do you have any idea what percentage of all these drugs has been to unapproved clinical studies?

Mr. **Davignon**. I have no idea whatever.

Senator **Hawkins**. I think it is obvious today that we know there has been far too little accountability in the use and distribution of these drugs. Would you not agree that we need better records?

Mr. **Davignon**. Well, I think a program the size of ours is always in the state of some change and some improvements, and in my own position, I have seen improvements evolve over the years that have been rather significant. We started out in the early sixties to the early seventies with manually operated systems of distribution. Now, we have been totally and completely computerized, relative to the distribution and the accountability of our drug products.

Senator **Hawkins**. According to my subcommittee staff study, you have been trying to design a more strict way to run your drug distribution program. Can you tell us what progress you have made toward improving the accountability of these drugs, and when will the system that you are designing be put into operation?

Mr. **Davignon**. Well, the system that has been discussed with your staff is the same system that Dr. Hoth has stated. We worked together in developing a system that could be used throughout the programs, and we are now implementing procedures and developing guidelines, to immediately get out to the investigators and to inform them just what we are doing. Responsibility in an investigational drug—there is a significant amount of responsibility of the investigator himself as he signs the investigative form. And we again feel that this is a training process with the many investigators that we have, and we are moving rapidly in this area.

[Information supplied for the record follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date August 20, 1981

From Chief, IDB, CTEP, DCT, NCI
Chief, PRB, DTP, DCT, NCI

Subject Response to Drug Distribution Policies Memorandum
Dated July 12, 1981

To Special Assistant for Clinical Affairs, DCT, NCI
Through: Associate Director, CTEP, DCT, NCI ______
Acting Associate Director, DTP, DCT, NCI ______

This memorandum describes our recommendations for improving the accountability and disposition of the use of investigational drugs. After considering several alternatives, including the possibility of satellite distribution centers, it is our consensus that the most practical alternative at this time is a system of strict accountability through improved recordkeeping by the investigators. Conceptually, this idea is based on the fact that investigational drugs are supplied by NCI to responsible investigators for the purpose of treatment of patients registered on approved protocols. Each investigator should, and is, in fact, responsible by Federal regulations to be accountable for his use of investigational drug by protocol. Therefore, in essence, each shipment of drug which is made to him should be accounted for according to its use and disposition for the patients entered on a particular protocol. Consequently, what is required is a logging system which details the patients entered on study. The key to this is that it can then be spot checked through the monitoring site visit progress as well as through review of periodic reports submitted to NCI.

We propose to implement a system of required recordkeeping by investigators or their designee (usually a pharmacy) which will be inspected at the time of site visits and which will be submitted on a periodic basis to NCI. The submission of accountability reports will serve as a condition for receiving further investigational drug supplies.

It is our belief that detailed record systems and periodic site visit reviews will serve not only to prevent diversion, but also will serve as an educational tool to remind the investigators that drugs are to be used on protocol patients. The key to this whole matter is the imposition of standard methods of recordkeeping by all sources utilizing NCI investigational drugs. It is through this standardization that we think we can achieve the control of these drugs as required in the existing and proposed FDA regulations.

Finally, we propose that this system be implemented in several steps with a trial period in certain institutions or cooperative groups and then phased-in across our entire clinical trials program. The initial step will take approximately six to eight months to implement. The final phase of all groups, contractors, guideline drugs, etc., may take as long as 18 months to fully implement.

This monitoring and accountability program requires a minimum of two additional professional staff members preferably a Commissioned Officer pharmacy or nurse type with clinical experience and background.

Attached are a series of outline forms and figures which further describe the objectives, needs and implementation of an accountability program for the Division of Cancer Treatment.

Daniel F. Hoth, M.D.

J Paul Davignon

J. Paul Davignon

Attachments

ACCOUNTABILITY AND DISPOSITION OF INVESTIGATIONAL DRUGS OVERVIEW

National Cancer Institute <------------------------> Clinical Investigators
(IND Sponsor)

- Provide investigational drugs for purpose of conducting research under approved protocols

- Account for receipt and dispensing of investigational drugs
- Return of unused drugs

ACCOUNTABILITY OF DRUG DISTRIBUTION

RESPONSIBILITIES OF INVESTIGATORS

FD-1573

"The investigator is required to maintain adequate records of the dispostion of all receipts of drug, including dates, quantities, and use by subjects, . . ."

OBJECTIVE:

Improve accountability of disposition of investigational agents.

NEED

- To comply with FDA regulations
- To assure that drugs are used for protocol research

PLAN

Implement a system of recordkeeping

- to be maintained by the investigator or his designee
- full accounting of the disposition of drug
- records will be available for inspection at site visit
- periodic reporting of the records to NCI

ACCOUNTABILITY OF DRUG DISTRIBUTION

RESPONSIBILITIES OF NCI

The sponsor shall:

A. "maintain personal contact with each investigator by visiting. . .the site of investigation. . . to assure that the following obligations of the investigator are being fulfilled:"

- maintenance of adequate records of
  - subject identification
  - clinical observations
  - laboratory tests
  - drug receipt and disposition

B. "these periodic visits shall include a review of the source documents. . ."

Source: Proposed FDA Regulations for Sponsors and Monitors of Clinical Investigations

ACCOUNTABILITY OF DRUG DISTRIBUTION

RESPONSIBILITIES OF INVESTIGATORS

"An investigator shall maintain adequate records showing the receipt and disposition of all supplies of a test article shipped to such investigator by the sponsor, including. . ."

- "quantities received"
- "each quantity dispensed with the identification of the subject who received it"
- "each quantity otherwise disposed of"

"The records required. . .are separate from and in addition to the records required for individual subjects. . ."

Source: Proposed FDA Regulations for Clinical Investigators

REPORTING REQUIREMENTS BY CLINICAL INVESTIGATOR

- Copies of logs will be retained according to FDA regulations
- Copies of logs will be forwarded to NCI at the end of each calendar quarter
- Further drug shipments by NCI will be contingent upon timely receipt of these records
- Logs should balance the quantities received with amount dispensed, disposed, and returned with the quantity on hand

RECORDS TO BE KEPT BY INVESTIGATOR
FOR EACH INVESTIGATIONAL DRUG

- A master log showing receipt of each shipment of Investigational Drug, the protocol for which it is intended, the lot number, the disposition of the drug, and current inventory.
- The record of disposition should showing the protocol, patient's identifier, date, amount, and investigator ordering the drug.

RECORDKEEPING AT NCI

- Receipt of logs at NCI will validate the continued shipment of drug to the investigator
- Logs will be filed by drug
- Spot checks of logs will be made on a random basis and compared with shipment records at NCI, and with information on hand regarding protocol status
- Reports from site visit teams concerning inspection of drug disposition records will be maintained by IDB. Discrepancies detected by site visits will be followed up by IDB staff.

DRUG UNITS* DISTRIBUTED IN SIX MONTH PERIOD
(January 1, 1981 - June 30, 1981)

Investigational Drugs Excluding Guideline and Commercial		250,873 (43%)
Guideline Drugs Only**		159,071 (28%)
Commercial Drugs***		170,448 (29%)
	Six Month Total	580,392

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*One unit = Vial, bottle or ampule

**Azacitidine
Erwinia Asparaginase
Hexamethylmelamine
Methyl CCNU
Streptozocin
THC
VP-16

***Commercial drugs will not have to be monitored

SIX MONTH DISTRIBUTION TO COOPERATIVE GROUPS

	All Drugs	Excludes Guideline and Commercial
ALB (Cancer and Leukemia Group B)	22,033	15,347
BRS (Cooperative Breast Cancer Group)	100	0
BTS (Brain Tumor Study Group)	4,930	2,625
CCA (Children's Cancer Study Group)	61,828	21,735
EOG (Eastern Cooperative Oncology Group)	32,875	12,402
COG (Gynecologic Oncology Group)	6,604	4,696
GRP (Intergroup)	1,604	20
NBC (National Bladder Cancer)	80	80
NCO (Northern California Oncology)	13,425	3,225
NCT (North Central Cancer Treatment Group)	998	252
PBC (Primary Breast Cancer Treatment Group)	27,932	1,555
POG (Pediatric Oncology Group)	15,387	8,527
RTO (Radiation Therapy Oncology Group)	4,918	4,865
SEG (Southeastern Cancer Study Group)	16,320	10,587
SWG (Southwestern Oncology Group)	27,219	13,122
TOTAL	236,253	99,038
Distribution to all other areas	344,139	151,905
TOTAL	580,392	250,943

IMPLEMENTAITON OF A PROGRAM FOR MONITORING INVESTIGATIONAL DRUGS

Step I.A. Development of a Pilot System

- Exclude guideline and commercial drugs.
- Develop monitoring and reporting forms.
- Develop distribution and disposition guidelines for investigators and other users.
- Institute a pilot program with one or two cooperative groups (or Cancer Centers).

Step I.B. Evaluation

- Evaluate feasibility and efficiency of the pilot program.
- Evaluate feasibility of dissemination of responsibility (decentralize) to groups such as the Cancer Centers and cooperative groups.
- Evaluate other approahces such as contracts.

Step II. Expand Program

- Expand program to all cooperative groups.
- Develop a program for all other groups such as the Cancer Centers, individual investigators, international groups, etc.
- Evaluate effectiveness and efficiency.

Step III. Full Implementation

- Include guideline drugs.
- Prepare operational procedures for FDA, investigators and administrators.

Senator HAWKINS. Thank you very much for joining us today, and we will excuse you at this time.

We have a final panel before the conclusion of our hearings today. We have another day of hearings, as you all know, on Friday.

Our next panel includes Mr. Edward Evans, Special Agent in Charge of the Washington Field Office, Office of HHS Inspector General, and Ms. Linda Little, Special Agent for the Washington Field Office.

If you would take your places rapidly, please. This will be a very short panel before our final panel.

Do you swear to tell the truth, the whole truth, and nothing but the truth, so help you God?

Mr. EVANS. I do.

Ms. LITTLE. I do.

Senator HAWKINS. Let the record reflect the witnesses replied in the affirmative.

Mr. Evans is Special Agent-in-Charge of the Washington Field Office for HHS Inspector General, and Ms. Little, as I stated, is Special Agent to the Washington Field Office. We appreciate your joining us today and staying this entire day. As you know, it is a very complicated subject, and I cannot be in a hurry to put the facts in the record we are trying to build.

I understand you both met with my subcommittee staff a few days ago, and you have heard the testimony of Dr. Hensley here today; is that correct?

Mr. EVANS. That is correct.

Ms. LITTLE. That is correct.

Senator HAWKINS. Regarding his referral to you of his findings on the use of methyl-CCNU.

Ms. Little, you attempted to pursue Dr. Hensley's referral after receiving it in October 1980; is that true?

Ms. LITTLE. That is true.

Senator HAWKINS. Can you tell what actions you took, what records you gathered and examined, and the number of individuals you interviewed, and when these interviews were conducted?

STATEMENT OF EDWARD M. EVANS, SPECIAL AGENT-IN-CHARGE, OFFICE OF THE INSPECTOR GENERAL, DEPARTMENT OF HEALTH AND HUMAN SERVICES, AND LINDA S. LITTLE, SPECIAL AGENT

Ms. LITTLE. After receiving Dr. Hensley's allegations, I discussed the matter with my supervisor, Mr. Evans. Because of manpower constraints at that time, I had to interview the one person that I was told had the most information. I interviewed a compliance officer who was involved with the inspections themselves.

Senator HAWKINS. Just one person?

Ms. LITTLE. That is correct.

Senator HAWKINS. Did you examine any records or any documents of any kind?

Ms. LITTLE. There were several documents, including some letters from the FDA to NCI.

Senator HAWKINS. Was that in March of this year?

Ms. LITTLE. That is correct.

Senator HAWKINS. Do you feel the methyl-CCNU matter should have been pursued at all?

Ms. LITTLE. We realized at the time that it was a very serious allegation and that it certainly deserved some attention.

Senator HAWKINS. Why did you feel that way?

Ms. LITTLE. First of all, the allegations that were presented to me by Dr. Hensley indicated certain violations—apparent violations—of title XXI. In addition to that, Dr. Hensley alleged a possible conspiracy that might exist.

It should be noted that the investigation of title XXI violations are the responsibility of the FDA and traditionally the Inspector General has not become involved in those violations unless there were clear indications that violations of title XVIII (criminal laws) had occurred. The possible conspiracy alleged by Dr. Hensley was not apparent in the allegations and it was no more apparent after an interview with the compliance officer who Dr. Hensley identified as having the most information in this matter. Because this matter was of such a serious nature, the Inspector General's Office could have broken tradition and done more preliminary investigation into this matter. However, because of manpower constraints, this was not possible.

Senator HAWKINS. Conspiracy?

Ms. LITTLE. Those were his words.

Senator HAWKINS. His words?

Ms. LITTLE. His words, because of the involvement of people in NCI, people in the FDA, and people from a laboratory which was sponsoring the studies.

Senator HAWKINS. Mr. Evans, was this case dropped?

Mr. EVANS. Yes, it was. That is, the criminal aspects of this investigation was closed by my Office.

Senator HAWKINS. When was it dropped?

Mr. EVANS. In June of 1981, we completed our investigation and forwarded the matter to the Health Care Systems Review Office, which is another component of the Inspector General's Office.

Senator HAWKINS. My subcommittee staff spoke to a Mr. Ronald Schwartz, who is head of the Inspector General's Health Care Systems Review Unit, and he said that his Unit did not pursue the merits of the methyl-CCNU case referred to him by your Office. Were you aware of this?

Mr. EVANS. I have been made aware of that today.

Senator HAWKINS. By whom? You were made aware of that today?

Mr. EVANS. Today. And last evening, I spoke to Mr. Schwartz, and I spoke to Mr. Michi, and I am now aware that they did not pursue this matter specifically, but in fact, they made this matter part of a preliminary management survey, which is now an informational paper to the Inspector General which will be the basis of discussions between the Inspector General and the Commissioner of FDA.

Senator HAWKINS. So Mr. Schwartz is the one who made you aware of this?

Mr. EVANS. That is correct.

Senator HAWKINS. Thank you both for your testimony. The subcommittee staff will be in touch with you.

[Information supplied for the record follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

NOV 13 1981

The Honorable Paula Hawkins
U. S. Senate
Washington, D.C. 20510

Dear Senator Hawkins:

In response to your letter of October 29, 1981 to Secretary Schweiker, I was pleased to be able to make Special Agents Ed Evans and Linda Little available to your Subcommittee during the November 3, 1981 hearing on the National Cancer Institute (NCI).

As Mr. Evans stated to you, his office received a number of allegations from a Department employee pertaining to possible conflict of interest or conspiracy on the part of employees of the Food and Drug Administration (FDA) or NCI, and other parties outside the Department, regarding the use of the drug Methyl CCNU. One of the statutory responsibilities of the Office of Inspector General is the investigation of allegations of criminality associated with programs and operations of the Department. According to standard procedures, the Office of Investigations (OI) therefore conducted a preliminary review of the charges made in this case. The review did not result in any findings which would indicate a violation of title 18 of the United States Code (the Federal Criminal Code).

As you know, the Federal Food, Drug, and Cosmetic Act of 1938 (title 21 of the U.S. Code) also prescribes criminal penalties for violations of certain regulatory requirements of the Act. Historically FDA has had primary responsibility for investigating alleged violations of title 21. Within the FDA, the Division of Scientific Investigations has its own staff of investigators (not under the supervision of the Office of Inspector General) who conduct investigations in response to complaints regarding firms or individuals doing research with new drugs. Those FDA investigators have been involved in an investigation that includes the allegations pertaining to Methyl CCNU. Based on the findings of our preliminary review, as well as limited staff resources within OI, other more pressing criminal investigations, and the fact that the Division of Scientific Investigations is responsible for determining if FDA regulations have been violated in a manner which suggests a potential criminal violation of title 21, we concluded that there were no circumstances in this particular case to justify further investigation by OI staff. Furthermore, we have no information which would cause us to question the finding of the FDA compliance officers assigned to this matter that there was no evidence to substantiate any allegations of criminal violations. Finally, we must defer to FDA on questions pertaining to enforcement of its regulatory program. Of course, we always stand ready to reopen an investigation if new information comes to our attention which indicates that further inquiry by OI agents would be appropriate.

I hope this elaboration of Mr. Evans' and Ms. Little's testimony is helpful to you and your Subcommittee as you continue to review this matter. If I can be of further assistance, please let me know.

Sincerely yours,

Richard P. Kusserow
Inspector General

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United States Senate

COMMITTEE ON LABOR AND
HUMAN RESOURCES
SUBCOMMITTEE ON INVESTIGATIONS
AND GENERAL OVERSIGHT
WASHINGTON, D.C. 20510

November 16, 1981

Mr. Richard P. Kusserow
Inspector General
Department of Health and
Human Services
Room 5250, HHS North Building
330 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Kusserow:

As Chairman of the Investigations and General Oversight Subcommittee, I am writing to request your assistance in the Subcommittee's investigation of the National Cancer Institute's drug development program and the regulation thereof by the Food and Drug Administration.

My request arises from certain information provided to Subcommittee staff by several of your subordinates. On October 29, 1981, Mr. Edward Evans, Special Agent in charge of the DHHS Inspector General's Washington, D.C. field office, and Ms. Linda Little, Special Agent for the same field office, informed Subcommittee staff of the following:

1. In October, 1980, the field office received from a source (Dr. Michael Hensley) at FDA a verbal referral alleging possible criminal activity in connection with the NCI's failure to promptly report to the FDA and to NCI-sponsored clinical investigators life-threatening and fatal reactions of patients administered nitrosourea anti-cancer drugs in clinical trial;

2. Ms. Little, the agent assigned to the case, stated that it seemed to be an "extremely serious matter" to her and worth pursuing, but, for lack of resources and because of another matter of higher priority, she conducted only one interview and was not able to review all of the documentation and materials relating to the case;

3. Mr. Evans stated that, on June 3, 1981, the nitrosourea case was referred to the Health Care Systems Review Unit in your office for investigation pursuant to Title 21 of the Code of Federal Regulations.

4. Both Mr. Evans and Ms. Little were under the impression that the nitrosourea case would be pursued by the Health Care Systems Review Unit.

As you know, Mr. Evans and Ms. Little provided this same information in sworn testimony to the Subcommittee on November 3, 1981.

On November 2, 1981, Mr. James F. Michie of the Subcommittee staff, telephoned Mr. Ronald D. Schwartz, Assistant Inspector General in charge of the Health Care Systems Unit. Mr. Schwartz provided Mr. Michie with the following information:

1. Mr. Schwartz's unit did not pursue the merits of the allegations pertaining to the nitrosourea case because, for lack of resources and expertise, his unit "had no way to do it".

2. Instead, Mr. Schwartz's unit "surveyed" the nitrosourea case, and a number of other such cases at FDA that had not resulted in prosecution, to determine whether the FDA had handled them properly; and

3. Mr. Schwartz submitted to your office an "informal" report on the findings of his "survey".

In light of the serious nature of these matters, it is essential to the Subcommittee's investigation that you provide me with two copies each of the following:

1. The memorandum report(s) of Ms. Little's interview(s) of Dr. Michael Hensley regarding the nitrosourea case;

2. The memorandum report(s) of Ms. Little's interview(s) with Robert F. Weidman, regarding the nitrosourea case;

3. The memorandum report, dated June 3, 1981, from Mr. Evans to the Deputy Assistant Inspector General for Investigations entitled, "Investigational Drug Branch,

NCI, NIH, PHS, DHHS, Bethesda, Md., Bristol Labs, Syracuse, N.Y. -- Possible conflict of interest; malfeasance WF-44-0-94-MIR Code 103 and attachments";

4. The "informal" report submitted to your office by Mr. Schwartz and pertaining to the "survey" of FDA investigations that did not result in prosecution; and

5. Any and all other documents and draft documents and written materials generated within your office and by any of your personnel and pertaining to the nitrosourea case and the Health Care Systems Unit's "survey" of FDA investigations that did not result in prosecution.

I would very much appreciate your providing me with these materials by November 20, 1981.

Should you have any questions regarding this request, please contact Mr. Michie of the Subcommittee staff at 224-8789.

Thank you for your cooperation in this matter.

Sincerely,

Paula Hawkins
United States Senator

PH: jm/tp

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

NOV 24 [illegible]

The Honorable Paula Hawkins
United States Senate
Washington, D.C. 20510

Dear Senator Hawkins:

I am responding to your letter of November 16, 1981, in which you requested several documents related to our investigation of the use of the drug Methyl CCNU under supervision of the National Cancer Institute (NCI) and the Food and Drug Administration (FDA).

Specifically, you requested the following items:

1. The memorandum report(s) of Ms. Little's interview(s) of Dr. Michael Hensley regarding the nitrosourea case;
2. The memorandum report(s) of Ms. Little's interview(s) with Robert F. Weidman regarding the nitrosourea case;
3. The memorandum report, dated June 3, 1981, from Mr. Evans to the Deputy Assistant Inspector General for Investigations entitled "Investigational Drug Branch, NCI, NIH, PHS, DHHS, Bethesda, MD, Bristol Labs, Syracuse, NY -- Possible conflict of interest; malfeasance WF-44-0-04-MIR Code 103 and attachments";
4. The "informal" report submitted by Mr. Schwartz and pertaining to the "survey" of FDA investigations that did not result in prosecution; and
5. Any and all other documents and draft documents and written materials generated within my office and by any of my personnel and pertaining to the nitrosourea case and the Health Care Systems Unit's "survey" of FDA investigations that did not result in prosecution.

Enclosed you will find the first three items you requested. Apparently, your request for the materials described under paragraphs 4 and 5, above, stems from a telephone conversation between Mr. Ronald Schwartz, Assistant Inspector General of Health Care and Systems Review (HCSR), and Mr. James F. Michie, of your Subcommittee staff. As a result of that conversation, Mr. Michie concluded that a report on this matter (or on FDA criminal investigations which did not result in prosecution) has been prepared by the HCSR staff of my office.

In fact, no such report has been prepared or submitted to me by my HCSR staff. However, I previously did instruct my audit staff to prepare a preliminary work plan for a survey of FDA management activities. The purpose of the survey would be to assist the Commissioner of FDA to make improvements where needed in FDA management operations. I have been briefed by my staff regarding the scope of the management survey we hope to perform. However the audit work plan itself is still being developed. Our plan to review the managerial aspects of FDA's regulatory program is unrelated to the allegations regarding Methyl CCNU. Rather, our sole objective is to work with the FDA Commissioner to improve the overall efficiency and effectiveness of his program.

I appreciate your interest in our activities, and hope I have been of assistance to you.

Sincerely yours,

Richard P. Kusserow
Inspector General

Enclosure

REPORT OF INVESTIGATION

Case Title:

INVESTIGATIONAL DRUG BRANCH
NATIONAL CANCER INSTITUTE (NCI)
NIH, PHS, DHHS
BETHESDA, MARYLAND
[illegible] LABORATORIES

File No: WF-44-0-94

Cross Reference Number:

Date of Report: JUN 3 1981

Type of Report: Closing

Character of Case: Possible Conflict of Interest/Malf

Report of S/A: Linda S. Little

Notice:

Closed in files of Washington Field Office. No apparent criminality.

Reports To:

1-HQ-OI
1-WFO-OI

Approvals:

Edward M. Evans
Edward M. Evans
Special Agent in Charge
Washington Field Office,

ASAC Initialed:

OFFICE OF INVESTIGATIONS

OFFICE OF INSPECTOR GENERAL
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Case Title: INVESTIGATIONAL DRUG BRANCH
National Cancer Institute (NCI)
NIH, PHS, DHHS
Bethesda, MD.
LABORATORIES

File No: WF-44-0-94

OFFICE OF INVESTIGATIONS
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

On October 24, 1980, a confidential source reported the following to Special Agents ROBERT A. SHERIDAN and LINDA S. LITTLE.

The NATIONAL CANCER INSTITUTE (NCI), NIH, PHS, DHHS, was granted an IND (#7631) as a sponsor for the testing of METHYL CCNU. The testing was performed by physicians at the NCI in the Investigational Drug Branch as well as by other physicians in other geographic locations. The substance was supplied by BRISTOL LABORATORIES. BRISTOL sponsored an NDA which was withdrawn in June 1978.

In September 1978, the DIVISION of SCIENTIFIC INVESTIGATIONS, BUREAU OF DRUGS, FDA, received a letter from the mother of a boy who had been treated with METHYL CCNU in chemotherapy. The boy developed severe renal failure and the mother wanted to know why she was not advised of that possible adverse effect on the IND consent form. It is a matter of record that earlier tests in animals indicated renal lesions; however, "many" of the consent forms in the IND failed to indicate that possibility, according to the source.

The DIVISION of SCIENTIFIC INVESTIGATIONS, as a result of inspections at BRISTOL and NCI, has evidence that the NDA and Annual Report to FDA in 1979 failed to disclose any apparent renal toxicity as a result of METHYL CCNU testing, although NCI now takes the position that they have received more recent information that it does have indications that renal toxicity has occurred. FDA has evidence that allegedly indicates that NCI knew of renal toxicity in 1977 and failed to promptly report that information to FDA.

The behavior on the part of BRISTOL and NCI, according to the source, appear to violate FDA regulations concerning reports of adverse effects. Moreover, the failure to report might also involve a conspiracy between NCI and BRISTOL.

However, even though there seem to be serious regulatory if not criminal wrongdoing involved here, the BUREAU OF DRUGS does not seem to be taking any action in this regard.

Investigation conducted on October 24, 1980 at Rockville, Maryland

by SA Linda Little, Robert Sheridan OI file number WF-44-0-94

Date dictated 03-31-81 Date transcribed 03-31-81 by MJG

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Office of Investigations

JUN -3 1981

Edward M. Evans Edward M. Evans
Special Agent in Charge
Washington Field Office, OI, OIG

Investigational Drug Branch, NCI, NIH,PPHS, DHHS, Bethesda, Maryland;
- Possible Conflict of Interest; Malfeasence
WF-44-0-94 -

Deputy Assistant Inspector General
for Investigations, OIG

In October 1980, a confidential source reported to this office that FDA inspections revealed that both NCI and Laboratories were in violation of FDA regulations by not reporting drug toxicity to the FDA. However, the source alleged that the Bureau of Drugs, FDA, for some unknown reason, was not taking action against the entities as required by Title 21 - Food and Drugs.

Briefly, Laboratories and NCI were involved in testing a drug called Methyl CCNU and related drugs. Both NCI and were aware of renal toxicity associated with Methyl CCNU at least in June 1978 and possibly prior to that. Neither NCI nor reported adverse effects to the FDA as required by law. The prescribed course of action in such a matter is withdrawal of all of s New Drug Applications (NDA's) relating to Methyl CCNU and related drugs. In addition, under current FDA regulations, FDA has the latitude to disqualify the clinical investigators in the study.

The inquiry conducted by WFO substantiated the failure to report adverse effects. This is a regulatory violation not within the scope of OIG authority. According to the compliance officer responsible for this matter, there is no evidence to support criminal violations in this case.

What seems to be left at issue is whether the system for regulatory action on the part of the Bureau of Drugs is so weak that no action whatsoever may come of this matter. The last FDA inspection relating to and NCI was done in June 1980. Since then, the Associate Commissioner for New Drug Evaluation has sent a letter and response to the FDA letter was received in January 1981. In the interim, withdrew its Methyl CCNU NDA and included a warning on package inserts. However, no other actions with regard to related NDA's has occurred. FDA is supposedly still "reviewing" the January letter from As for NCI, no action has occurred.

In view of the apparent regulatory deficiencies present in this matter, it may be appropriate to have this matter reviewed by the Division of Health Care and Systems Review, OIC.

WFO/OI:LITTLE:MJG 05-29-81

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
WFO	Little	6/2						
WFO	[illegible]	[illegible]						

OFFICE OF INVESTIGATIONS
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

On March 4, 1981, [redacted], [redacted], DIVISION OF SCIENTIFIC INVESTIGATIONS, OFFICE OF THE ASSOCIATE COMMISSIONER FOR NEW DRUG EVALUATION, BUREAU OF DRUGS, FDA, Rockville, Maryland, was interviewed at the ROCKVILLE, SUB-OFFICE, WFO, OI, OIG, by Special Agent LINDA S. LITTLE. Mr. WEIDMAN stated substantially as follows:

He was involved with inspections at BRISTOL LABORATORIES in New York and inspections at the NATIONAL CANCER INSTITUTE (NCI) in 1980 as a result of a consumer complaint regarding renal toxicity associated with the substance Methyl CCNU. Methyl CCNU had been approved by FDA NDA's about a year prior BRISTOL's withdrawal of the NDA on 6-15-78 because an FDA ONCOLOGY REVIEW COMMITTEE determined that there was no increase in survival attributable to the product.

In February 1980, BRISTOL was initially inspected by FDA to determine when BRISTOL, the NDA sponsor, first learned of renal toxicity. BRISTOL officials said that NCI, the IND holder and drug testing sponsor, notified them by a letter dated sometime in March 1979 of renal toxicity. The letter was signed by a Dr. JENSEN-AKULA.

During a June 1980 inspection at NCI, FDA was shown a copy of a letter dated 6-15-78 from Dr. A.T. TURISSI, NCI to BRISTOL, reporting renal toxicity.

Upon recontacting BRISTOL, FDA was told that upon subsequent search of their files, they located the letter in question. There was no explanation as to why that letter was not available during the initial BRISTOL inspection.

As a result of these events, [redacted] advised that both NCI and BRISTOL had a responsibility to report the adverse reactions to FDA. He opined that the evidence gathered as a result of the aforementioned inspections is suggestive but not supportive of 18 U.S.C. violations and the matter, therefore, is not being pursued in that direction.

The ultimate responsibility for determining what action FDA will take against BRISTOL and/or NCI rests with Dr. MARION J. FINKEL, Associate Director, NEW DRUG EVALUATION. To date, Dr. FINKEL has sent BRISTOL a letter advising BRISTOL of its apparent failure to report to the NDA significant findings as a result of the testing of Methyl CCNU and other related substances. [redacted] added that realistically, FDA is limited in the actions it can take against NCI (e.g., one federal agency charging another federal agency with regulatory violations).

In January 1981, BRISTOL responded to the FDA letter pointing out deficiencies. BRISTO reply included a statement that any failure to report was negated by a 1980 labelling change warning of renal toxicity.

BRISTOL's response is still being "reviewed" to determine if their response is "sufficient." [redacted] said there is no way to predict how much longer the "review" process will take and he added that the option available to the agency is the termination of all related NDA's. This would require a hearing, but he does not know if the NDA's will be terminated by FDA.

Investigation conducted on March 4, 1981 at Rockville, Maryland
by SA Linda S. Little OI file number WF-44-0-94
Date dictated 03-31-81 Date transcribed 03-31-81 by MJG

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Senator **Hawkins**. Now, we will have our final panel. The final panel is four physicians who have been directly involved in anticancer chemotherapy: Dr. Charles Young of the Sloan-Kettering Memorial Cancer Institute; Dr. John Durant; Dr. John Speer, and Dr. Emil Frei.

I appreciate your patience in waiting to testify here today, and I know that your work in fighting cancer through chemotherapy has given you confidence that this kind of treatment can be a lifesaver. I know your thoughts and I share your optimism regarding the promise that chemotherapy has shown. I want to congratulate all of you on your progress.

But do you share my concern—and I will ask each of you this—that there are occasions where abuse might go undetected because of lack of proper oversight, and if you share that concern, how can this problem be corrected? We will start with Dr. Frei.

STATEMENTS OF DR. CHARLES W. YOUNG, MEMORIAL SLOAN-KETTERING CANCER CENTER; DR. JOHN DURANT, UNIVERSITY OF ALABAMA; DR. JOHN SPEER, COLORADO SPRINGS, COLO.; AND DR. EMIL FREI, THE SIDNEY FARBER INSTITUTE

Dr. **Frei**. Well, to be sure, I know I speak for the panel in saying that we share that concern, and we have heard some things today that are of concern. I would emphasize that, because of that concern, a fairly substantial tightening of the regulations was rendered 2 years ago. There are now some 8 or 10 contractors who do phase I studies. All of these people are picked competitively. They are high quality individuals, scientifically, clinically, ethically. They represent major institutions with the resources to do the study. This monitoring system involves an ongoing review at specified intervals of all patients and their flow sheets. This should have a major impact but it is too early to tell. But we do have a relatively new system in force, and I would propose that we see how well it works before we add additional things.

Senator **Hawkins**. Do any of you have anything you would like to add? Dr. Durant?

Dr. **Durant**. I would like to add to Dr. Frei's remarks by indicating that we have been sufficiently concerned to attempt to develop a computerized system which would make functional an online reporting system for all data within 24 hours for clinical studies function. And the National Cancer Institute has funded us to develop that system, and we are currently implementing it in our own institution and within the past month, have expanded it to several related institutions—the University of Florida being one—and we believe we have clear evidence that the use of that system clearly reduces inadvertent errors and probably will prevent most advertent errors. And I would like to stress that there are practically no advertent errors.

Senator **Hawkins**. Thank you.

Dr. **Young**?

Dr. Young. I agree that there certainly is a continuing, let us say, drive on the part of physicians to innovate in therapy sometimes without going through the process of filling out the proper forms. Over the period of time that I have been closely involved with the phase I work, this tendency has been markedly reduced. I believe that the group at the NCI has played a very major role in improving the quality control within the phase I working group; they have also had a major impact on protocol design.

Like Dr. Durant, by the use of computer technology, we are progressively shifting from retrospective quality control to prospective, ongoing, online, quality control not merely to see that inappropriate studies do not get started—we have regulatory mechanisms within the center to prevent this kind of thing—but to see that the tests that are written into the protocol are obtained at the proper times. And in this regard, the clinical trials monitoring service has played a very useful role. They have given us all grades, if your grades in terms of the expected frequencies of observations do not match what you consider to be your standards, you feel a real compulsion to improve.

I feel that there is a continuing interaction within this community that is moving in just the direction that you wish it to.

Senator HAWKINS. Dr. Speer.

Dr. SPEER. Well, I, unlike the other members of the panel, come from a community cancer center, as opposed to a major cancer center, and I can tell you that we share the same concern about monitoring of investigational things that we participate in. And it is interesting that even we in a community center have gravitated in the same direction and are in the process of putting together a computer system to monitor and record data on all of our patients who are on various studies.

I think that the most important monitor that I know of for the new things that are done to my patients is myself, in that I really am, No. 1, concerned about them and their welfare, and I took an oath as a physician when I graduated from medical school, and I am very concerned about their welfare. And I think that certainly, if I, No. 1, do not do a good job in being greatly concerned and very cautious about the welfare of each of my patients that no one external to me can certainly do it around me. So I welcome, certainly, outside help, objective, nonparticipating monitoring of my activity, as I know everyone else does. But I think it is important that, No. 1, I have to do a good job.

Senator HAWKINS. Do you mind if anyone looks at your records?

Dr. SPEER. No, I do not. As a matter of fact, the FDA did come to our hospital and do a review of our study that involved methyl-CCNU about a year or a year and a half ago, and they looked at all our records, and I was a little apprehensive at first, them coming to do that. I do not think I had any problems with them looking at all of our records, and they did so.

Senator HAWKINS. I imagine they learned a lot from looking at your records. Are you concerned that maybe, as a physician, you do not get all the information that is available?

Dr. SPEER. What kind of——

Senator HAWKINS. As we have heard today, if you have listened to all the testimony here today, there may be some information drawn that is not disseminated to the physicians.

Dr. SPEER. That certainly is a major concern that I have and I think, everybody else has, and so it is a major effort on our part that we do expend to try to find out the information that there is available. Certainly, investigational drug that we have received from the NCI and have used in protocols—I have been an independent investigator, using a number of drugs, for sometime, a program, as you have heard before, which is coming to a close. But we have always had the drug brochure to go over all of the animal toxicity studies and all of the previous clinical trial data before we write out protocols, so that information has always been made available to me—that plus, of course, reports in the literature from conferences and other things that we attend.

Senator HAWKINS. That is a lot to read, I imagine, and keep up with.

Dr. SPEER. It is tough. It is exceptionally tough.

Senator HAWKINS. Dr. Durant, tell me a little bit about the computer program that you put into place at the University of Alabama and you say the University of Florida now has.

Dr. DURANT. In our university, Dr. David Wertchafter, who is an information specialist and a pediatrician, originally working with babies with jaundice in high-risk nurseries, worked out a program for managing many babies by what is called an algorythm and developed a system, which anybody can learn to use, whereby the computer asks you only those questions necessary to make decisions and requires you to put the data in before the decision is made, and like Dr. Young's system, the computer is programed so that unusual values are asked to be checked, the data is printed out immediately, it can be dumped overnight to a central computer so that we can get data from all the institutions and all the stations participating in the study. The equipment costs about $20,000 per institution, and almost anybody can learn to use it. There is a great deal of programing yet to be done, because each new study requires a few changes in the program. But we are encouraged by our initial efforts. We think we have clearly demonstrated that inadvertent errors were virtually eliminated by the system. We also did use a similar paper system, with physicians in the State of Alabama, and they performed every bit as well in a drug program as any investigator I have been associated with.

So we believe the system has great promise. It has still got a lot of work to be done on it, but the NCI has seen the promise in that, too, and has given us satisfactory funding for development.

Senator HAWKINS. Dr. Frei, do you believe that as currently structured, the drug development program is skewed too heavily on the side of caution or avoidance of risk to patients at the expense of progress and innovation?

Dr. FREI. Well, there is the potential of an adverse relationship, of course, between regulation and creativity, and while we have made a great deal of progress in cancer chemotherapy and therapeutic research in cancer generally, we still obviously have a long way to go.

I think the new regulations—not new, but the modification of the regulations that have come in force in the last 2 years—are reasonably adequate and should be given a trial, and I suspect will be much more effective and much tighter than those in the past. I do not see that they will inhibit creativity. But that is something, very obviously, that we must be concerned about. I would not like to see a whole new layer of investigation and supervision imposed upon us before the one that has been laid out in the past 1½ years has had a chance to function and hopefully, function effectively.

Senator HAWKINS. How long would that take?

Dr. FREI. Five years.

Senator HAWKINS. Five years?

Dr. FREI. Yes.

Senator KENNEDY. Madam Chairman, could the others respond on that same question? Could we hear the rest of the panel?

Senator HAWKINS. Surely. Dr. Durant?

Senator KENNEDY. Do you agree or disagree?

Dr. DURANT. I agree.

Dr. YOUNG. As it currently functions, I believe that the program makes every effort to encourage creativity, but also to control it—not to have a series of disconnected impulse-type protocols, but to welcome innovation and to channel it properly, facilitating communication within the community, so that it is not done just at a single center, but that innovative approaches can be shared.

I feel that certainly, the Clinical Trials Monitoring Service has been a welcome addition. We have learned from it, in terms of keeping our data, and we look forward to further collaboration with this idea.

I, for one, do not wish to be released from regulation. Each of us is part of a community, and within our community, we have those who urge haste and those who urge caution. By the negotiation process, we move in a consistent direction. Frankly, the threat of review by the Food and Drug Administration, or the threat of having grants cut off, is a useful tool in controlling an individual who wishes to go outside of our usual channels.

I think that the regulations that we have probably function fairly well. Although we have heard this morning and have read elsewhere of isolated instances wherein they did not function as effectively as we would have wished.

In terms of my own actions, I think they function fairly well.

Dr. SPEER. Well, I think that I am always much more afraid of whether I have done something wrong in relationship to the regulators—the NCI, the FDA, and all those people—than I am afraid of what is going to happen to my patients. I sit down with my patients and discuss things very frankly with them, and we know basically what we are getting into, at least in a partnership type of way.

I think it is good for me to be a little fearful of the system because it does keep me honest, it does provide me with some discipline from the outside to regulate what I do, so I am not disturbed with the kind of regulation that there is at the present moment. I am concerned, like Dr. Frei said, in other levels of regulatory kinds of things. But I do not think there is any problem with the NCI not making available new drugs to places like community cancer centers like ourselves. I think that is best done in major cancer centers. I think much of the system as it functions is very good.

Senator HAWKINS. Last week, one of your colleagues said, and I quote, "Regulations are toxic." Do you agree? I did not detect that in any of your comments.

Dr. **Speer.** Well, I think that creativity is associated with an impulsiveness, and that good science is also associated with discipline. So that Dr. Frei said, you know, you are tempted to be creative impulsively, yet one has to be very systematic and disciplined in order to be at your best scientifically. That is really the conflict that we have within ourselves and that we all have in relationship to the system. And it is a difficult conflict, and it is one that is a problem that will always be there, and it is probably healthy, I think, as Dr. Young said.

Dr. **Frei.** It seems to me the distinction has to be between effective and appropriate regulation, which all of us would agree to. Overregulation, or counterregulation, or the superimposition of successive regulations at intervals that do not allow for the evaluation of the previous one is counterproductive to our creativity. And I think we should reevaluate the current monitoring and regulation system only after sufficient time has passed to allow evaluation.

Senator **Hawkins.** Would any or all of you like to respond as to your individual impressions of the testimony you have heard here today, during this long hearing? Will anybody volunteer what your impressions were of this hearing and the testimony you heard here?

Dr. **Young.** I believe that the individuals speaking here addressed their concerns in an honest and effective fashion. It was not as sensational or black and white as some of the recent press presentations have been.

I think that the point has come out clearly from a number of voices that all drug trials are therapeutic drug trials, this included phase I trials. As a physician, I could not approach the bedside and ask a patient to take something that I did not believe was in that patient's benefit. I mean that patient, not future generations and so forth, but that individual. I think that this message has come through, both from family members and from physicians. I think the Food and Drug Administration, as evidenced by Dr. Hensley's comments concerning therapeutic research, is aware of the intense difficulty under which we are trying to make progress.

From that point of view, I feel these have been good and useful hearings. Some deviations from proper form have been disclosed, and these have been and should be pointed out and should be corrected, both by structural changes to prevent them from occurring, such as the insistence on the use of an internal review boards, and the insistence on use of clearing a protocol with the sponsoring agency before it is activated. These points have been effectively made.

Senator **Hawkins.** Dr. Durant?

Dr. **Durant.** May I further address or amplify what Dr. Young said in regard to therapeutic research, and that is that the results that will be obtained with many of these drugs used in phase I trials therapeutically are not nearly as good as they will be by the time those same drugs are advanced to be used in patients who have not been previously treated. So that looking for high response rates in phase I trials is asking a great deal. There are usually response rates because the drugs have been advanced to those trials on the basis of very good animal information. But to look for phenomenal results in a phase I trial is usually asking too much of that trial, because the patient being treated usually has had heavy prior therapy and would not be expected to have as good a response as if that patient had never been treated. But it is not reasonable to use many of these drugs in previously untreated patients, because there are established therapies that such patients often should receive first.

Senator **Hawkins**. Dr. Frei?

Dr. **Frei**. I think that is a very important point. It is important to appreciate the setting of a patient with advanced cancer who has become refractory to all known effective treatment. It is extraordinarily complex and the informed consent situation is complex. The ultimate toxicity to the patient in terms of morbidity and mortality is the tumor. When you introduce a drug you frequently have problems of interpretation. I think it is important to emphasize that some 150 drugs have been introduced into phase I trial in the past 25 years. Of this, 30 to 40, or approximately 30 percent, have proven effective in the treatment of one or more forms of cancer and have been commercially approved. Therefore a patient does have a one chance in four of receiving an active drug.

So there is the positive of it, in a situation where otherwise, there is really very little, if no hope. And phase I studies not only involve new drugs. They can involve the use of established drugs in combinations, in new ways. In that setting, there are two or three circumstances where patients in phase I clinical trial were cured by that phase I treatment. That was true for Hodgkin's Disease, it has been true in testicular cancer, and I am sure it is going to be true increasingly in the future.

Senator **Hawkins**. Thank you.

Senator Kennedy.

Senator **Kennedy**. Just to continue, I want to welcome the panel to our hearing. I think we are fortunate to have your comments. This is an extremely distinguished panel, and I think the contributions of all of you have certainly made a very important positive impact on many people in need in our society.

I want to extend a special warm welcome to Dr. Frei, who I have known over a number of years and who heads one of our great medical centers in Boston and was the general supervising doctor in my son, Teddy's, case. So I have had a good chance to know Dr. Frei over a number of years and have experienced many of these questions that we are talking about here in generalities, in a very particular way. I am glad that we are having your testimony on the panel.

Let me ask you just with regard to phase I, I would like to get brief responses from all of you on the phase I trials, about when you are using these extremely powerful drugs and they are being first used and tested in human beings. How do you in your own mind balance the potential for science and on the other side, the anguish, the pain, and the suffering of an individual—and is it really worth it in terms of the progress for science. I would like to get you all on the record on that point.

Dr. **Frei**. Thank you, Senator, for your warm comments. I would say under all circumstances—and I speak for all of us, and I think the investigative cancer community—that our primary concern has to be for the patient in front of us. We may be asking a scientific question, but that must be secondary. If that patient with advanced cancer takes a position that makes it clear that he would not like further treatment, having been told that there is no further known effective treatment, that is the position that we would support.

On the other hand, there are many families and many patients who cannot close the door of hope, and that door of hope has to be some kind of new treatment. And we would offer him, if we have a new treatment that we think might be effective, some kind of new treatment. I indicated that the past record of our drugs is that one new drug in four turns out to be active in the clinic—so there is realistically an element of hope. To offer, to even suggest that that is a curative intent situation would be inappropriate. But patients in that circumstance usually do not ask that. All they want is to know that there is something new and promising concerning which there is a reasonable chance that they might respond. Now, that reasonable chance—1 percent, 5 percent, 25 percent—we cannot deal in those numbers because we do not know. On the other hand, if it is a patient, for example, for whom there are several new drugs that are active, and you are doing a phase I study of active new agents used in combination, that has been successful in the past in terms of curative treatment. As as I emphasized, in some phase I studies in the past, such new combinations have in fact proven curative to patients in phase I trials.

So I would say first and foremost, we are concerned about the patient in front of us. We are obviously concerned about the patients we are going to see down the line, and it is not very often, in my judgment, that those two concerns are mutually antagonistic. Almost always, they are supplementary. I would not want to talk a patient into new treatment who clearly psychologically was not prepared for it. It would not be good for that patient.

Senator KENNEDY. Dr. Durant?

Dr. DURANT. I agree with everything that Dr. Frei has said. I would like to provide an anecdote in regard to a personal patient who I entered into a phase I trial, a combination of BCNU and procarbazine, almost 10 years ago. He had been continually sick with Hodgkin's Disease for 2 or 3 years. That phase I trial cured him, and he is now bored with coming back to see us, and is doing well. In that same study which was subsequently published in "Cancer", several other patients were also cured of their disease by that phase I trial that was run long enough ago to make sure of the curative potential. So it really exists.

On the other hand, we have more trouble keeping patients from going into inappropriate studies on their own desire. An important part of a discussion is, "Is this trial appropriate for you?" And the patient is much more likely to ask for inappropriate therapy than that it be proposed to him or her.

Senator KENNEDY. Dr. Young?

Dr. YOUNG. The balance between humanism and science is a critical one. We have to live with it on an everyday basis. As I indicated before, if we offer a phase I drug to a patient, it is because at that particular point in time, we feel that that is more likely to provide a response in that individual than the other conventional agents alone or in combination that we have available to us.

The question of cure—though all of us have actually seen cures with phase I trials—is not quite so important as is useful prolongation of life. One of the speakers earlier today noted that she had seen one of the children graduate from graduate school. This is the kind of goal—a very human goal, that an individual can strive for and hope to obtain useful prolongation of life, even out of a rather new drug.

But how much are we deluding ourselves? At least in part because of these hearings, we added up the results of our phase I studies since 1976. Out of 929 patients, on phase I drugs, we have had 106, or about 11.4 percent, in whom we saw objective, antitumor effects. This included 30 complete or partial remissions which were of clear benefit to the patients. This was done at the cost of nine probable drug deaths, or approximately a 1 percent mortality rate. And as you hear extensively earlier today, three of those drug deaths were from one drug. DCF.

Therefore, I do not think that that is a self-delusional system, and it is not one that I need to depart from too quickly.

Senator KENNEDY. Dr. Speer?

Dr. SPEER. Well, I think that one point that is worthwhile making is we have heard the term used today on a number of occasions, "experimental drugs." I do not like that term, because "experimental drug" suggests that it is used in experiment. But we know that experiments are what we do to guinea pigs, and the difference is that I do not care about any guinea pigs. They are not important to me. But our patients are important. I think it is a major difference. I myself like the term, "investigational drug," rather than "experimental drug," because it says that what we are doing is an investigation; we are looking at something new. The important thing, though, is that at that point in time, that seems to be the very best thing there is to do for that patient. And that is what physicians are all about, as opposed to scientists. Physicians' jobs are to do what they think is the very best thing for the patient at hand. A scientist's job is to discover new things. Now, we want to discover as much new as we can. One, however, has to compromise the opportunity to discover new things for the sake of the patient on many occasions. And so science is not as pure in the practice of medicine as one would like for it to be. It is not pure as it would be and is in the laboratory. It is the toughest kind of science to do because of that problem.

But I think that all physicians who are involved in investigational treatments, whether it be phase I, phase II, or phase III trials, pilot studies—you name them, whatever they are—investigational treatments are really meant to be in the very best interest of each patient on an individualized basis.

Senator KENNEDY. Let me ask, is there any substitute for phase I trials? How else would you be able to acquire that kind of knowledge?

Dr. SPEER. Well, I have heard Dr. Frei say this, and I would defer to him. I think that phase I trials are absolutely critical in the job that we have, because if we had not had all the phase I trials on all the drugs that we have presently available to us that work very well, we would never be where we are, so we have got to keep doing that.

Senator **Kennedy**. Does all the panel agree with that?

Dr. **Frei**. Yes.

Dr. **Durant**. Yes.

Dr. **Young**. Could we just expand that a bit? Some human being has to be the first patient to get a drug; whether you call it phase I or initial, some human being has to be the first patient. The phrase "phase I" came in, at least in part, in an effort to provide some internal structure and discipline to what up to that point had been a fairly casual process; that is, beginning a patient on a drug, giving him some the next day, a little bit more the third day, and so forth. This was done in a fairly episodic fashion, taking a very considerable period of time, and, frankly, without adequate controls for safety. The whole discipline of a structured phase I trial was organized to try to enhance the safety factor and to increase productivity.

Senator **Kennedy**. Would all of you agree that in any either phase I or investigative drug trial, that the patient ought to be given full information as to what the effects or potential side effects should be? Would you all agree with that?

Dr. **Young**. There is complete accord on this. I have in the formal testimony two documents that address this. We are in complete agreement with you.

Dr. **Frei**. Well, Senator, let me say that it happens not infrequently that a patient is referred with advanced refractory cancer, an appropriate candidate for a phase I trial who wants a phase I trial. But there are patients who would like to know everything in detail about what is being offered them. But there are also some patients who say, "You are the doctor. I come to you because I have faith in you or your institution. I would be just as happy not to know all of those details."

Now, I am not sure what one does about the right of the patient not to know. By law we must—and we do—discuss the protocol with the patient and show them the written informed consent. They read it. I think most patients like that probably do not read it very carefully. But I say that to indicate the absolutely full range of complexity of the situation we are talking about.

Senator **Kennedy**. That would be a decision that would be made by the patient, what you have just referred to—am I correct—the decision would be made by the patient that either they want to know more or they want to know less.

Dr. **Frei**. That is right.

Senator **Kennedy**. But as far as all of you are concerned, and as far as you know the profession, they believe that all of the patients and their families ought to have full and complete information and the most up-to-date information on whatever phase I investigative drug is being used.

Dr. **Frei**. Absolutely.

Senator **Kennedy**. Second, do you all agree that in the investigative research that all adverse effects should be fully and completely reported?

Dr. **Durant**. Absolutely. As indicated by some of the NCI staff, it may be very difficult to distinguish an adverse effect of the treatment from an adverse effect of the disease, and clearly, the answer to that question has to be tempered with clinical judgment, or one will overwhelm the system with information, which will then become garbage, and nobody will be able to make any sense out of it.

So there is no question about informing—concerning adverse events, but if you raise the background noise by informing about everything bad that happens, you have got a hard problem.

Dr. **Frei**. This is a slightly tangential answer to the question. But I do not think any of us take the adverse effects lying down. You asked is there a substitute for a phase I clinical trial; there is not. But the science of tumor biology and clinical oncology is moving very rapidly, and the compounds that come into the clinic in the future almost certainly will have greater specificity for the tumor and less toxicity for the host. I would predict in 5 or 10 years, there is going to be a marked trend in that direction.

Second, we have—all of us and others—mounted major research programs designed to minimize the side effects; that is, the toxic effects, of cancer chemotherapeutic agents. And we have made considerable progress in reducing very substantially nausea and vomiting, in using Adreamycin or Adreamycin analogs in ways that produce less cardio-toxicity, and such things as blood products to prevent the adverse effects of chemotherapeutic agents on the marrow.

So we do not accept the toxic effects. We are working very hard on those in an effort to minimize them, either by treatment of the toxic effect itself, or by developing drugs which produce less in the way of side effects and more in the way of destruction of the tumor.

Senator **Kennedy**. Let me ask you, can you identify any specific areas of excesses and abuses in the national cancer program, and if so, what would they be?

Dr. **Young**. This may be a strange answer, but to some degree, you are asking us to testify against ourselves. I feel that I contribute to the national cancer program. That program is not just the NCI. We are all part of a research community. When I do research under NCI sponsorship, I believe that they do research. I have always felt that within the cancer research community there was receptivity to ideas from many quarters.

I think that the excesses and the deviations that we hear about arise from individuals with excess therapeutic zeal that do need to be reined in. But I think that these are exceptions. I think that overall, the system functions remarkably well, and I think its premier status in the world is an indication of just how well it functions.

Dr. **Speer**. I think there is an area that is important than in the past was probably lacking to some extent, but which is in the process of changing rapidly, and that is the appropriate transfer of all this information into the community, into the hands of doctors who take care of the majority of the patients. I am in one of those communities, so I am very aware of those kinds of problems.

We have taken major pains, and it has been a major effort to be involved in investigational things in a community hospital. It has, however, been recently our fortune to receive a grant from the

National Cancer Institute for a community hospital oncology program, and I think that has been of major benefit to us in helping organize a mechanism to disseminate new educational information to doctors in the entire community, which almost certainly will result in the upgrading of the patients' care.

I would think that the thing that, from my point of view, is more important is to work on new methods of getting the community involved in the national cancer program. I know Dr. DeVita is very concerned about that, and some steps are underway.

Dr. **DURANT**. I would like to make sure you do not misunderstand. We do not have individual scientific and sometimes administrative differences with the people who manage the National Cancer Institute, as is appropriate in any free forum. But if you are talking about excesses or scandals, I think that is a very different issue from legitimate differences that there might be between political parties.

Senator **KENNEDY**. There have been a series of articles that appeared in the Washington Post about patients seeking cancer treatment involving chemotherapy. What impact does a series like that have on patients and their families?

Dr. **FREI**. Senator, I believe it has a very profound and adverse impact on patients and families. I know that, because those articles were reprinted in the Boston Globe. And I had many patients who may have been somewhat insecure to begin with, but whose insecurity in terms of their treatment was maximized. They were anxious, their families were anxious. And it is not only patients on phase I studies. There were several circumstances in Boston where patients on what is known to be curative treatment with chemotherapy for certain diseases had their treatment interrupted because of their interpretation of what was a very anecdotal, biased, inappropriate, sensation-seeking article, as far as I am concerned.

It not only affects current patients, but also affects families of patients who have died in the past. If a patient goes on experimental treatment, and the family and everybody has agreed to that, and the patient does not make it and perhaps had some toxicity, then there is always concern as to whether that was the right thing to do. There is some guilt. After a period of time, that goes away and is placed in perspective. But those articles in the Washington Post brought it back in full play. And I think the damage that was done over the country was enormous.

That might be an appropriate price to pay where there is something positive to come out of the articles. If they interviewed the same proportion of patients who are cured of their cancer by chemotherapy as the very few patients who might have serious or fatal toxic manifestations because of their chemotherapy—that is, if it had that kind of balance——that would have been appropriate. But it was a thoroughly unbalanced article and, I would say again, had a very adverse effect on patients and families.

Dr. **SPEER**. The comment I heard that probably best describes those is that it very well might be more toxic than all of the toxic chemotherapy, because there is the real potential that patients will die as a result of deciding not to receive treatment now, and they very well might be greater in number than the 620 patients supposedly who died of toxic chemotherapy.

Dr. Young. In at least one circumstance that I am aware of, they made selective use of the information available to them. A colleague of mine spoke with them on the telephone, in my hearing, giving favorable results of a drug, methyl-glycyl-bis-guanal-hydrazone, or methyl-GAG, in some considerable detail. It now looks to be a significantly useful drug in the treatment of malignant lymphoma. There was no mention of this in the version of the report that was published in Washington, D.C. It did occur in a deprecatory fashion in the wire service and was mentioned in a Florida paper—I have copies of both of these—in addition to the necessary documentation with regard to the efficacy of the drug, if you wish them.

Dr. Durant. I have given to your staff, Senator, a copy of a letter written by Dr. Vogel from the University of Miami in Florida, that I would like to be written into the record. I will not read the letter, but the gist of it is that almost everything he says was taken out of context, and most of the patient information was severely slanted. There is no point in reading that whole letter. It has been written to the Washington Post editors, but I would like it read into the record.

Senator Kennedy. Well, we will have an opportunity to see what the Washington Post writes tomorrow as a result of your testimony and statement.

Let me just ask a final question. I was going to ask whether you thought that those particular cases that were raised in the article were the exception to the rule, but I think I heard in response to an earlier question that you thought it was mainly anecdotal. I do not know if there is anything that you want to add. I think you have made general comments about the articles, which I think are important to have on the record. But I do not know whether there is anything on that that you want to bother adding. I think you addressed the series in a framework which I think has been constructive and positive.

Dr. Young. I think one can say that if the articles had given a realistic idea of the state of cancer research in this country, we would not have been here voluntarily; you would have had to have subpenaed us.

Senator Kennedy. I think that is helpful.

Finally, maybe in a very brief way—because I am sure you could talk for a long period of time, each of you—you could comment on the progress that you have seen as a result of the use of chemotherapy in the patients who have been affected by cancer. Could you give us at least a brief comment on that?

Dr. Frei. Well, Senator, as a result of phase I studies over the past 25 years, some 30 to 40 agents have been identified—that is, medicines or drug—which are active against one or more forms of cancer. By taking those and often putting them together in combination, it has been possible to devise curative programs involving chemotherapy only, or chemotherapy plus surgery and radiotherapy for some 14 forms of human cancer. This has resulted in a 25-percent decline in mortality from cancer in subjects in the United States under the age of 45. We do better in younger people and that is better, because they have a much greater life ahead of them. We are beginning to do better in older patients, as well. So we are making progress.

I think it is very important, however, that the revolution in the science of molecular biology is spilling now in a major way into tumor biology. And what we know about cancer today at a molecular level—that is, at a basic level—is probably twice what we knew only 3 or 4 years ago. These include techniques involving recombinant DNA, monoclonal antibody production, both of which have a potential for producing much more specific antitumor agents—that is, agents much more effective against the tumor and much less adversely effective against normal tissues.

So I think the progress we have seen in the recent past is only the beginning.

Dr. DURANT. Also, I would like to call to your attention and it is in my written testimony that Dr. Phillip Cole of our institution, formerly of Dr. Frei's institution—we stole him—is in the process of preparing a paper which I think will document that our progress has really been a lot more than we have been able to appreciate.

There has been a steadily falling mortality rate in the United States since 1968. As a matter of fact, it amounts to .75 percent a year. The major reason for that is a fall in deaths from the major cause, cardiovascular disease, but the fall in death rate from cancer has kept pace with the fall in the death rate from cardiovascular disease. The net change in the relative survival is zero. However, the real change or improvement in survival because of that is more than 5 percent.

Dr. YOUNG. I think you are all familiar with the therapeutic advances in leukemia, lymphoma, tumors in children, and the more recent breast cancer data. To me, the most encouraging things are that we are beginning to make progress in lung cancer, esophageal cancer, and that we are also finding more effective ways of combating the side effects, as Dr. Frei has mentioned. I feel we now have a good anti-emetic agent—not perfect, but one that really has some effect.

Dr. SPEER. Well, when you ask the question, what is the effect of chemotherapy in relationship to what I do, I can tell you that it is certainly the most exciting thing that I know about. I have been at Penrose Cancer Hospital now for 6 years, and I virtually do nothing but treat patients with chemotherapy. And I think that a little over 25 percent of my patients now come back to my clinic to see me after the completion of all chemotherapy, many of them who almost certainly are cured, and a good number of them who have a very high likelihood of being cured because they are progressively farther from their treatment, and that is very exciting.

When I started out as a Fellow—and I have not been doing this too long—I went to M. D. Anderson Hospital 9 years ago and started out on the acute leukemia service—two patients died the first day I was there, and in the course of 6 months on that service, I saw a large number of patients die.

I think the progress that has just been made in the time that I have been in this field have been very exciting and very impressive.

So I think chemotherapy is a major important modality. It certainly cannot be given successfully without significant side effects and toxicity, because chemotherapy only works when it is given in large enough doses to kill cells, and those kinds of doses cause side effects. But I think that patients who go through chemotherapy who are alive to tell about it, like the patients we saw this morning, can really tell you the story best. It is very difficult. It is exceptionally hard. I do not understand how hard it is. I see these patients all the time, but I do not think I have any idea of how difficult it is. But they are all happy for every day that they are alive.

I recently had a fellow who is 21 now. He developed acute leukemia at age 16. He came to see me, and he now is on an annual follow-up basis. And he told me that he thinks the best thing that ever happened to him was that he got leukemia, because at age 16, he was on drugs, and he quit high school, and after he went into remission, he got his high school degree, he is now in college working on a business degree and working full-time as well. He says, "You know, every day is really important to me." I have a good number of patients like that, so I think chemotherapy is exceptionally important.

[The prepared statements of Dr. Young and Dr. Durant follow:]

TESTIMONY

BEFORE THE

INVESTIGATIONS AND GENERAL OVERSIGHT SUBCOMMITTEE

OF THE

SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES

SENATOR PAULA HAWKINS (R-FLA), CHAIRPERSON

CHARLES W. YOUNG, M.D.

CHIEF, DEVELOPMENTAL CHEMOTHERAPY SERVICE, DEPARTMENT OF MEDICINE

MEMORIAL SLOAN-KETTERING CANCER CENTER

NEW YORK, N.Y.

NOVEMBER 3, 1981

Madame Chairperson and Members of the Subcommittee:

I am pleased to have the opportunity to discuss with you the status of this country's research program in new anticancer drugs with particular emphasis on its ethical basis, its performance over the past decade and its prospects for the future.

My name is Charles W. Young. I am a physician, board certified in Internal Medicine and in Medical Oncology. I have participated in clinical and laboratory research on new anticancer drugs since 1959. Since July 1976 I have been the Acting Chief and then Chief of the Developmental Chemotherapy Service at Memorial Sloan-Kettering Cancer Center. This is the clinical service at our Center that is responsible for initial evaluation of new cytotoxic anticancer agents. Since July 1976 our Center has participated in 26 Phase I studies on cytotoxic agents and in 3 Phase I studies on antiemetic agents. Since 1977 we have published or have in press the primary results of 17 Phase I and 41 Phase II investigations in this area.

THE ETHICAL BASIS AND THE QUALITY OF ETHICAL PERFORMANCE IN NEW DRUG STUDIES

Because the currently available drugs do not cure all cancers, major therapeutic improvement can only come from the development of new drugs. Each of these must have an initial clinical trial under intense medical supervision which we term the Phase I evaluation. The proper dose-effect relationships of all of the current useful cancer chemotherapeutic medications were developed in Phase I studies; they are absolutely necessary first steps for the clinical use of any candidate new drug. If we are to make continued progress in cancer research there can be no disagreement on this point; new drug studies including Phase I trials must continue. As humans, and particularly as physicians, there also can be no disagreement that these studies must be ethically sound and in accord with the highest moral principles of our society both in concept and practice.

New drugs should be given to cancer patients in Phase I only with therapeutic intent both on the part of the patient and the physician! This is not a new idea; it is inherent in the very concept of the role of the physician and in the nature of the doctor - patient relationship. You have seen reports that "the primary purpose of a Phase I study is to determine toxicities and dose levels, not to treat the patient".[1] I find that proposition unacceptable and unrealistic. I could not offer or administer a drug to a patient if I had no hope that that specific individual could benefit thereby. I believe that the vast majority of my colleagues entering patients into new drug studies are of this opinion and act in this manner. I base this statement on my personal observations over a period of years of my own actions and those of my colleagues, at the bedside, in protocol design and analysis and in selection of drugs for study within the Center. Those new drugs with strong laboratory credentials for therapeutic benefit and promising results in clinical trials outside the United States are highly sought after by multiple Centers. Protocol design that minimizes the likelihood of individual patient benefit is scrupulously avoided. Observations with regard to possible therapeutic effects are pursued assiduously in all phases of drug study. In the early phases of a study where hope is high, the rate of patient accrual is rapid; when objective antitumor effects are observed, the rate of patient entry into study accelerates. If and when a patient's condition progresses to a point where we find no hope for therapeutic benefit we do not offer further drug treatments; rather, we provide compassionate bedside attendance and comfort to the patient and the family.

Earlier this year I wrote an editorial entitled "Science, Humanism and the Phase I trial"[2], as a contribution to a continuing discussion on the very question we are considering this morning. I provide a copy of that editorial for inclusion in the record. Noting that some individuals find Phase I trials of anticancer agents an uncomfortable scientific necessity because the likelihood of patient benefit is small, the editorial urged that it is ethically appropriate to administer a potentially toxic new drug to cancer patients, "not because they are in such dire circumstances that they have nothing to lose, but rather because they might hope to benefit from the drug's anticancer effects". When we ask a patient to take an experimental drug rather than a conventional drug or combination of drugs, it is because we believe that for that patient the experimental drug with an unknown result holds more therapeutic promise than treatments that have failed repeatedly in similar circumstances. It is tragic when a patient's disease progresses in spite of therapy; it is not acceptable to a thoughtful physician for this to occur repeatedly in the same way without trying a new therapeutic approach. Although the likelihood of a cure is small with any single agent therapy, useful prolongation of life and comfort is still a desirable goal and one that is achievable for at least some patients entering a Phase I drug trial.

We have an obligation to assure that the patient consent for experimental therapy is as fully informed as possible. Up to 1/3 of the time of our

Clinical Investigation Committee, (our ethical review body), is spent discussing and requesting modifications of the patient consent forms for protocol studies. Since 1978 the Psychosocial Collaborative Oncology Group, including Memorial Sloan-Kettering Cancer Center, the University of Rochester Medical Center and the Johns Hopkins University School of Medicine, has been carrying out a detailed study of the Informed Consent process. This is one of a number of studies funded under NCI Grant CA19681 to PSYCOG. I provide for the record a preliminary report of that study entitled "Patients' Perception of Giving Informed Consent for Investigational Chemotherapy". The results of this study are meaningful in light of our current discussion. The patients entered into treatment because they sought to benefit thereby and had trust in the physicians who were caring for them.

The consent form inself provided a context and an agenda for the interaction between the patient and physician but the physician's recommendation was the most important factor listed in the patient's decision. In view of this strong reliance on the physician, it is worth noting that 69% of the interviewed physicians who had secured these consents believed that their patients would obtain substantial benefit from treatment; 99% believed that the potential for benefit at least outweighed the potential liabilities of treatment.[3] On the negative side, when interviewed 1 to 3 weeks after signing consent, the study discloses that although 98% of patients remembered being told of the possible risks and side-effects they exhibited poor recall of their precise nature and only 69% remembered being told of the research nature of the treatment. The results of this study will help us strengthen the patient education aspects of the consent process.

PRACTICAL RESULTS OF NEW DRUG RESEARCH IN RELATION TO ITS TOXIC BURDEN

We have tabulated the results of our Center's Phase I studies of cytotoxic drugs in non-leukemic adults from 1976 to the present. We have treated 929 patients; we observed 106 patients, 11.4%, in whom there was objective anti-tumor effect, including 30 complete or partial remissions producing clear benefit to the patient. Among these 929 patients there were only 9 patients or .97% in whom drug therapy was probably the cause of death. These data clearly establish that Phase I drug studies can be carried out without inordinate risk to patients and strongly suggest that for the patient there is a significantly greater chance of benefit than of serious injury.

The studies at our Center with Gallium Nitrate illustrate the therapeutic potential inherent in some new drugs and emphasize the importance of obtaining an optimal dosage schedule through Phase I evaluation. We first began to study the drug in 1977 in Phase I under NCI sponsorship, giving the drug primarily by brief intravenous injection on a weekly basis. Out initial study included 51 adults; it obtained 1 partial remission and 8 minor regressions and demonstrated that the drug produced reversible kidney injury. Believing that Gallium might be more effective when administered by a continuous infusion over 7 days we recently extended our Phase I study by this schedule. We have now completed the infusion Phase I evaluation treating 45 additional patients. Twenty-seven patients with measurable disease are evaluable for therapeutic response; in this group we have obtained 1 complete remission and 10 partial remission for a 41% major response rate. Four of 9 patients with non-measurable disease have also experienced subjective improvement and an improved performance status. There were no drug-related deaths in our Gallium studies. We expect to evaluate Gallium by this schedule in a series of Phase II studies in the coming years; we suspect that it may prove to be an agent with major utility.

At the urging of the staff of the Investigational Drug Branch of NCI we have recently re-evaluated the drug Methylglyoxal-bis(guanylhydrazone) known by the colloquial and somewhat unfortunate term of MethylGAG. Considered active but excessively toxic two decades ago it was rescued from obscurity by Dr. William Knight and by pharmacologic demonstration that it is slowly cleared from the body requiring a weekly or fortnightly schedule of administration. When given in this fashion we have obtained 18 partial remissions in 46 evaluable heavily pretreated patients with malignant lymphoma, a 39% useful remission rate with no drug mortality.[4] MethylGAG will shortly be evaluated as part of initial combined therapy for patients with a malignant lymphoma and a poor prognosis.

I would like now to discuss briefly a developing success story that illustrates the fact that progress in cancer results from the actions of an entire community of scientists and that it is a continuum with later events building upon earlier observations. Cisplatin is now recognized as a remarkably useful drug in the management of testicular and ovarian cancer; it has lesser activity in other tumors as well. Earlier in its clinical evaluation cisplatin was nearly abandoned because of the unacceptable renal toxicity and severe nausea and vomiting it produced. Cvitkovic and Hayes then at our Center demonstrated in dogs[5] and then in a Phase I trial in humans[6] that the renal toxicity could be greatly reduced by vigorous hydration prior to, during, and after administration of cisplatin. These observations led to the changed administration techniques that permit the drug's current wide usage.

Cisplatin has only modest therapeutic activity in lung cancer and in esophageal cancer, however when combined with vindesine, a new drug with moderate activity as a single agent in these disorders, major therapeutic improvement appears possible. The combination of vindesine and cisplatin at our Center has produced a 43% complete and partial remission rate in 85 patients with advanced lung cancer and a 21.7 month median survival of the responding group who received larger doses of cisplatin.[7] The combination of cisplatin, vindesine, and bleomycin produced partial remission in 21 of 40, i.e. 52%, patients with esophageal cancer.[8] Thus by the combined use of these newer drugs we are beginning to produce major therapeutic effects in these common tumors that were previously non-responsive to therapy.

The nausea and vomiting that is so troublesome with cisplatin and many other cancer chemotherapeutic drugs is also beginning to respond to treatment. Metoclopramide, an antivomiting drug widely used in Europe, is not effective in low oral doses in managing chemotherapy-induced vomiting. Noting that this drug can abolish cisplatin-induced vomiting in dogs at large intravenous doses, Gralla and his colleagues at our Center carried out a dose finding study of intravenous Metoclopramide, establishing that a dose 7 times greater than the usual oral dose could be given with safety and apparent useful effect.[9] They then established tne superiority of this regimen by direct comparison with the most commonly used antiemetic agent.[10]

I would like to conclude by noting that in the area of new drug research the American cancer research community is preemenent in the world.

In achieving this position the Federal Government through National Cancer Institute has played and continues to play an absolutely vital role.

It provides the vast majority of the research funds; it provides the majority of the new drugs; it provides essential leadership and guidance. It provides the means and mechanisms by which we have formed ourselves into a research community. At the level of clinical trials the staff of the National Cancer Institute are effective colleagues. Without being restrictive to our creativity they have greatly enhanced the precision and the research quality of our protocol design. They have properly advocated completed meaningful studies rather than a series of disconnected "pilot" probes. I have found them prompt to report possible unexpected drug toxicity to me or from me to my co-researchers at the other Centers. None of us should be exempt from criticism, but particularly considering the magnitude of the task and their limited staff I believe they do an excellent job.

Madame Chairperson, I am grateful to you and to the Subcommittee for the opportunity to discuss these matters with you.

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TESTIMONY

BEFORE THE

INVESTIGATIONS AND GENERAL OVERSIGHT SUBCOMMITTEE

OF THE

SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES

SENATOR PAULA HAWKINS (R-FLA), CHAIR~~PERSON~~

JOHN DURANT, M.D.

UNIVERSITY OF ALABAMA

NOVEMBER 3, 1981

Gentlemen:

I want to address my remarks today about the extreme importance of the National Cancer Institute's Drug Development Program from two vantage points - the first as someone whose entire professional career has been spent trying to improve treatment for cancer; the second, perhaps, more important, as the husband of a victim, the brother of another, and the good friend of a third. You see, my wife has breast cancer; my sister, 4 years younger than I, has chronic myelogenous leukemia; and my friend and trusted employee for the past 12 years has cancer of the colon.

Over the past 10 years, we have accumulated increasing evidence that patients who have cancers which are responsive to drugs can be cured when two or more drugs are added to local surgery or radiation. New drugs are badly needed as additional tools in order to treat the whole patient. Surgery alone, radiation alone, or a single drug alone cannot be relied upon to treat more than perhaps 1/4 of patients, that 1/4 that until recently made up the cured fraction of patients.

Because of this at the University of Alabama in Birmingham and in the Southeastern Cancer Study Group, of which I am Chairman, we have been involved in early studies of many drugs for the treatment of cancer and its complications.

The studies that first convinced the FDA that Ara-A could be safely given were done in our Center on cancer patients with only a few months to live and who were told there was virtually no chance the drug would help them, but that it might help others. Today, because of those studies, patients with cancer who get shingles have less pain and less chance of dying from dissemination of the shingles while in remission. Babies with disseminated herpes simplex with and without encephalitis can now be saved to live a normal life. Similarly, we determined the tolerable dose of Acyclovir in patients with cancer who were told there was more chance of toxicity than benefit. Because of this, we believe we have the ability to prevent fatal or disabling herpetic infection in patients undergoing marrow transplantation and in thousands of lymphoma, Hodgkin's disease, and other cancer patients.

We have also been involved in early trials of 5-Azacytidine for acute leukemia, AMSA, Mitoxantrone, and now Bisantrene. Three of these four drugs appear to have important therapeutic activity. Are these trials ethical when toxicity may occur without therapeutic effect? Until a better system is proposed, and I know of none, the answer must be "yes". The benefits far outweigh any risks. I will try to explain why. Because of FDA rules, these drugs must be started at doses so low that responses cannot be expected and toxicity is rare. Thus, response rates in these studies are always lower than would be expected if all patients were treated with full doses. Many of us would like to start with higher but still safe doses that might produce more responses. Response rates in these early studies have little meaning because previously treated patients, the only ones usually permitted in these studies, have much lower response rates than those with the same disease who have never before been treated. Would you test drugs in the previously untreated? The state of the art now requires that multiple drugs, most not curative by themselves, be put together and used earlier and earlier to obtain curative therapy. Seldom do we find a single new drug that offers the potential to do the job alone. Frequently, however, we find new drugs that when added to others already known, are capable of inducing cure. Others will testify as to the importance of this process.

The toxicity of treatment is acute, dramatic, and usually transient. The benefit is substantial, enduring, and continues to increase as noted in the recent Newsweek article of November 2, 1981. It is this substantial benefit which clearly supports the current process. I want to concentrate on explaining why at our Center we believe the present NCI method of calculating survival considerably under estimates the beneficial effects already achieved by treatment. Dr. Philip Cole, Associate Director of Epidemiology in our Center and formerly at the Harvard School of Public Health, is working on a scholarly paper that will document one point. You are, no doubt, already familiar with the probability that the present method of calculating the cost of living increase overestimates the rate of inflation. In the case of cancer statistics, the current method of calculating survival undoubtedly under estimates results because of three problems. For you to assess whether the early trials now in dispute are worthwhile, it is necessary to understand how far we have come.

The first problem is that relative survivals are used. These are not corrected for the decade. You already know that deaths from cancer in children have fallen by nearly one-half. That has been easy to detect because cancer is the most important cause of death in children over two years of age. However, since relative survival is used, as the population ages and cardiovascular disease becomes the commonest cause of death, cancer mortality is now influenced by that from heart disease and the many other causes of death in the elderly. This is important because from 1950 to 1967 the all-cause death rate in the U. S. was nearly constant. But in 1968 and subsequently the all-cause death rate began to decline by about 0.75% per year...amounting, by 1960, to a 10-12% reduction in mortality in just 12 years. The major reason for this is the decline of nearly 1.5% per year in deaths due to coronary artery disease and stroke.

The relative survival rate is a statistic which corrects for competing causes of death; it is an effort to assess the increased risk of dying due to the specific cause of interest. Since mortality from heart disease has decreased by about 20% in the past 13 years, cancer mortality would have to fall equivalently, as it has, for the relative survival figures from cancer to remain unchanged, as they have. This bias prevents a real decrease of approximately 5% in cancer mortality from being detected.

Second, the average age of the cancer patient at diagnosis has increased by 11 years while that of the general population has increased by only 6 years. Thus, people are generally 5 years older at diagnosis than in 1968. As they age, they are gradually more frail and less likely to survive any disease or treatment and improvement overall is harder to obtain. Phase I trials are not conducted in these patients.

The third factor obscuring an understanding of the real impact of improved survival is, ironically, that in 1950 some patients were already cured. Twenty-five percent is the usual estimate of patients cured in the pre-chemotherapy era. Now more than 40% are cured. This apparent 15% improvement has occurred, obviously, by improving the results only in those 75% who previously would have died. This means that survival has actually been improved by 20%.

We estimate that if the calculations were made correctly as a result of considering all these factors, the correct current relative survival would be between 45% and 50%. I would like to stress again that, since overall mortality from all causes is dramatically dropping, we must take this into account in assessing results reported from only one cause. It is this benefit that is increasing and, in my mind, far out weighs the toxicity.

More important to me, however, than new drugs, new treatments, and better statistics is what can be done for my family and friend. My friend and trusted colleague of 12 years is now participating in a phase I-II trial of liver perfusion using a new device. Her participation was at my advice, and I am happy to report we have strong evidence of a favorable response. My sister has not needed treatment during the past year. I am hoping that research may offer something of real value when she does need it again. Finally, my wife has written you a letter about her experience that I would like to read you. It summarizes my position better than I could say and puts the entire issue of drug development into human terms.

November 1, 1981

Dear Distinguished Senators:

I had my breast removed 19 months ago in April, 1980 when I was 41. The cancer was already in my armpit. I woke up to the terror of cancer and fear of death. As I am married to an expert in oncology and since I attended medical school, worked in cancer research both at St. Jude Children's Research Hospital and the University of Alabama in Birmingham, I was very aware of the realities of a future with cancer. My house and my head have been filled with cancer patients through the years. I was told there was hope if I went through chemotherapy. It would not be easy, but without the treatment, I would have much less chance of cure and the almost certain recurrence that ultimately meant death.

As I see it, I had no choice - I will fight for my life - even as those many people who first took the same drugs I was given in a last ditch fight for their lives. Because of their fight, their courage, I have real hope - not complete assurance but real hope that I may be cured.

My daughter, Jennie, was 3 years old at the time of my diagnosis, surgery, and treatment. I have real hope to be with her in her growing years, to be the one to guide and teach her as she grows to adulthood. I have real hope of sharing a relationship and growing old with my mate and partner.

The side effects of chemotherapy were terribly hard. They were worth that chance of living. I experienced nausea with a capital NAUSEA. The first time, I stopped counting after 25 times of vigorous vomiting for three hours. Each treatment was followed by 10-14 hours of vomiting, then 10 days of 24 hours/day nausea. I then had 10 days of gradually feeling better, and it was time for another treatment. None of the current antinauseants helped much. I would lie in bed thinking and feeling that a battle was being fought in every cell of this body that is me - and I was not sure I would win. My mental picture saw the drugs washing through my toes, ears, hair follicles, every part of me and meeting those cancer cells with the only weapon we know. And that weapon I owe to people willing to fight and take even those small odds with the new drugs found by research.

My hair fell out - all of it. I had explained to Jennie that the strong medicine I was taking to make me well would also make me sick and bald. When she saw the hair coming out combfull by combfull until it was all in the sink, she said, "Mommie, your hair is coming out." I answered through clenched teeth, "Yes, and I hate it." Her response, "Mommie, I love you."

Doesn't this put the whole awful cancer treatment in a nutshell and in the correct perspective?

Those of us who have cancer want the chance to continue our lives. What we must go through to have this hope, this promise of future, "Mommie, I love you's", "Wife, I love you", and from us, "Life, I love you" is hard, uncomfortable at best, but worth the agonies. I thank God that Adriamycin, Cytoxan, and radiation were possible for me, and I thank research and all those people with so little hope but with the courage to fight for my chance to live and who first took those drugs.

I pray that drug development research will not just be allowed to continue as it is, but will be augmented so that the real hope I have may be turned into certain cure for many others.

Respectfully and sincerely,

Marlene Durant

Comprehensive Cancer Center for the State of Florida

October 24, 1981

Editor, Washington Post
1150 15th Street, Northwest
Washington, D.C. 20071

Dear Sir:

The Washington Post story entitled "The World of Shattered Hopes" dealing with patients treated at the Comprehensive Cancer Center for the State of Florida, while largely factual, is written with considerable negative bias and ommission of critical points which alter circumstances as they actually occurred. The statements and facts were taken out of context and crucial words omitted so that misinformation was conveyed to your readers.

Before addressing individual inconsistencies, the obvious negative bias of the reporters is deserving of comment. This issue has been adequately addressed by Dr. DeVita in his letters to you and by Tom Brokaw in his recent television interview with the reporters. Additional emphasis on this unfortunate negative bias deserves repetition. Although it is true that no patient in the IMPY Phase I study done at the University of Miami had an objective antitumor response as rigidly defined in the protocol, our publication in Cancer Treatment Reports, Volume 64: page 1153, 1980, clearly states that two patients had clinically useful improvements. One patient with lung cancer had an improved appetite and a sixteen pound weight gain with a period of disease control lasting for six and one half months, directly attributable to treatment with IMPY. A second patient with a surgically unresectable cancer in the head and neck region had enough improvement and shrinkage in his tumor to allow for surgical excision that improved his performance status and quality of life for many months. While the authors commented on some of the patients receiving another investigational drug, ICRF-187, who had appeared to benefit little from the drug, no mention at all is made of another patient with malignant melanoma who did have an objective response to treatment and, indeed, has been maintained on treatment with continuing disease control for almost one year, with minimal drug-induced toxicity, Since the authors have chosen to include Aminoglutethimide and Provera as investigational agents (although they have been widely used for two years) one might wonder why they focus on two patients (one of whom may have had a toxic reaction to these drugs) when the literature is replete with scores of patients who have had objective antitumor responses, prolongation of life, and relief of symptoms from these drugs when used in the managements of breast cancer.

In almost all of the clinical histories related by the authors, major omissions of information have probably already led to inappropriate bias. Because consent for the use of patient names was approved by the patient or family members and because your reporters have already mentioned them, I shall refer to the case histories by name. In the case of Jerry McClennan, the authors refer to a symptom complex occurring on January 22, in vivid and graphic detail. What they fail to make note of is the fact that no such reaction occurred on his two previous doses of drug and none occurred during his last dose of drug on January 29. The principal investigator of

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study was informed of the reaction and during the next administration the patient was watched closely for any signs of acute toxicity and there were none. It is possible that this reaction was related to the rate of drug infusion; however this type or reaction has never been seen in any other patient treated with this drug at our institution, and, as previously stated, was encountered only once in Mr. McClennan's use. It is also of interest to note, that in spite of Mr. McClennan's apparently adverse reaction to this investigational drug he subsequently elected to receive still another investigational drug, mitoxantrone, at a later date.

In the case of Harvey Mottaz the investigational drug had indeed caused an objective antitumor response and with no nausea, vomiting, or bone marrow suppression. The patient had a very large tumor on the side of his face causing severe pain. After only one dose of drug the tumor size dramatically decreased and the pain virtually disappeared. This response, although impressive was of short duration and he was considered to have had progressive disease after a total of 69 days. The patient's attending physician, Dr. Mario Eisenberger, clearly recalls the objective and subjective benefits to the patient even though it was for a brief period of time. What the reporters stress, however, is their first visit to Mr. Mottaz on January 15, 1981, where they state that "the day before he had been given more chemotherapy" (possibily implying some other investigational drug). At that time Mr. Mottaz had progressive disease and was starting to recover from acute toxicity of Cisplatin, a standard drug in the management of head and neck cancer, and not an investigational drug. It is indeed ironic that just the preceeding day the authors had commented on Cisplatin as a "success story", yet it was this standard drug and not an investigational drug that had caused the toxicity that the reporters decry. The quotations attributed to the patient's wife are also misleading because they do not refer specifically to the investigational drug. Our medical records clearly show that Mr. Mottaz developed no significant toxicity from the drug other than the hair loss and specifically no nausea or vomiting. The comment by the intern, Dr. Feldman, unfortunately is typical of the reaction of many young physicians and lay people alike about chemotherapy in general. His comments were fittingly dramatic and graphic for inclusion in an article with the very bias the authors were trying graphically to emphasize.

In discussing Margaretha Gaylord the authors once again neglected to mention the fact that while the drug did not stop the inexorable down hill course of her cancer it also did not cause any significant toxicity to the patient. Her death was clearly related to disease progression in the brain and not to any toxicities attributable to the drug.

In the case of Annie Laurie the extent of bone disease secondary to breast cancer was one of the most severe I had ever seen. In a telephone conversation with the patient's son, Mark, on October 23, 1981, he recalls that she had already been told by her oncologist in West Palm Beach that he had nothing more to offer. The patient had a zest for life, a fear of death, and a desire to try anything that could stem the course of her cancer. She had been suffering from severe bone pain and had received so much x-ray therapy to relieve that pain that further chemotherapy was out of the question because of compromised bone marrow function. Although the patient had not had a definite response to several previous forms of hormonal therapy she had had transient improvement of pain on Estrogens, suggesting some possibility of hormonal sensititivity of the tumor. Aminoglutethimide was a logical treatment to try. This drug was considered by many oncologists, even at that time, more as a "standard" therapy, although it had not yet officially been released for commercial use. It is now available commercially, testifying to its widespread efficacy in the management of breast cancer. The quotation "But I never considered going off it. This went on for four months . . . Why? Because the doctor said it takes that long to find out if it works." implies that we were keeping her on an investigational drug to gain scientific information perhaps at the expense of the patient's well being. In fact, we were the only people in Florida with ready access to this investigational drug which we were making available to qualified oncologists more as a humanitarian gesture than any scientific study. An Informed Consent Form had to be signed because the drug was "investigational", however, she was not part of any Cancer Center study aimed at future publication or scientific aggrandizement of the Center. As for her and her daughter's recollection of the side effects of the drug the medical record has a somewhat different account. The patient was begun on the Drug on August 21, 1980, and over the next four months travelled with her family to Acapulco, the Bahamas, and Jamaica. Medical records document that she benefitted by having decreased bone pain although she was suffering from depression. At a six week evaluation x-rays were also found to be stable. In the face of stable disease on x-ray and decreasing bone pain, a further six week trial was recommended and accepted by the patient. It was we who told the patient that some of her symptoms of depression might have been due to the drug. Yet it remains equally possible, as her son Mark now relates, that she was becoming depressed because she sensed the end was near and that she was going to die. When the patient was taken off the drug on December 19, 1980, there was either a misquote according to the author's bias, or misrecollection on the part of the patient. The quote states "we have a new thing on the market . . . we would like you to try it". At that time the situation was closely analogous to the situation with aminoglutethimide, She had exhaused all avenues of treatment except perhaps for removal of her adrenal glands or pituitary gland, both major surgical procedures. There were exciting reports from Italy of high dose Provera given intramuscularly being highly successful treatment even with patients with far advanced disease. We had embarked on a study of high dose Provera in an oral form and had already treated some patients who had had objective anti-tumor responses and, to that point, no toxicity at all. The patient took the drug for three days and graphically related the symptoms she had experienced. The cause for the symptoms are uncertain since they abated after she stopped the drug and she did not return to our care but rather stayed in West Palm Beach under the care of her physician. The dramatic increase in pain could have been due to what we call a pain flare from the hormone or perhaps exacerbation of the disease (a known complication of hormone therapy in breast cancer) or a true side effect of the drug (perhaps some spasms of the blood vessels leading to the brain).

On reading the authors' statements about Annie Laurie's recollections of her treatments I personally was hurt and my staff was deeply concerned because the article implies an impersonal rendering of investigational treatment. What she actually received was a very personal brand of medicine with drugs of considerable promise given in a humanitarian and not truly, investigative setting. Having concerns about our doctor-patient relationship, I called Mark Laurie on October 23, 1981, and asked him for his impressions of his mother's feeling about the care rendered at the Comprehensive Cancer Center for the State of Florida. His quotation was "she loved you guys down there". Does the casual reader carry that away from your author's version?

In the section on "The Director", two studied omissions have potentially dangerous implications. First, "I would kill myself" leaves out all of the provisos . . . far advanced disease, intractable pain, or other incapacitating symptoms in addition to the stated proviso of "lack of effective standard therapies", it is my recollection that I said, "I might consider suicide" in such a setting.

In the paragraph stating "Vogel said" the omission of the phrase "Phase I Drugs" leads the reader to the erroneous conclusion that Dr. Vogel feels that all drugs have a very low chance of success which is clearly not the case since chemotherapy is ~~curable~~ curative for a number of cancers as attested to by Dr. DeVita's previous comments.

Finally, several paragraphs on protocol conformity and recording errors, imply widespread and frequent inconsistencies. A review of those allegations is underway and to date a few inconsistencies have been found, but these are isolated and sporadic. In the ICRF-187 study, which is being carefully monitored by the National Cancer Institute and G.H. Besselaar Associates, the compliance rating of the Comprehensive Cancer Center for the State of Florida with protocol requirements stands among the highest of all centers being monitored (third out of 50 monitored). I believe that the DMPY data have the same degree of protocol conformity and that the conclusions drawn were justified by the data and methods used.

The authors Ted Gup and Jonathan Newman came to our center as wolves in sheeps' clothing. They questioned me and my staff about the pressures in the emotionally trying profession we had chosen. They were "sympathetic" with "burnout" among nursing personnel dealing day in and day out with cancer patients. They saw at first hand the loving care that was given to our patients whether they were on investigational drugs or standard therapies. Yet, none of this was dealt with except in the very briefest passing statements leaving the overall impression in the minds of most readers who have contacted me, of a heartless, soulless group of diabolical "investigators".

Ted Gup and Jonathan Newman have done cancer research and the dedicated people involved in it considerable harm and have put me and my already physically and emotionally depleted staff under dramatically increased stress. We feel deceived and disappointed that they could write such a story with such a negative bias after seeing clinical cancer research at first hand, essentially censoring most of its positive features.

Sincerely,

Dr Chas L Vogel

Charles L. Vogel, M.D.
Clinical Director

CLV/jc

Senator **Kennedy**. I want to thank you all very much.

Senator **Hawkins**. Thank you very much.

I think we have heard a lot of good here today, and we have also heard some of the bad. I reviewed the original mission of the war on cancer. It was for early detection, diagnosis and therapy, prevention, education, and rehabilitation, which are the five components of the 1971 Cancer Act.

The good side, as you have talked about, Dr. Speer, are those who have hope and opportunity because of remission. I think some of the bad we have heard here today would be the lack of dissemination of information to doctors like yourself, who need it on the local level; cancer patients and their families not being able to get the entire facts when they are looking for them. Probably the most damaging thing we have heard here today came from the agencies, designed to work together for the benefit of patients, who have been unable or unwilling to establish an effective dialogue. The Senator and I talked about some ways that we might be able to stop that impasse. I know that the American public is looking to this subcommittee for changes that will bring solutions to cancer.

We are going to continue this hearing on Friday morning at 9 a.m. At that time we will hear from the highest level of officials who administer the anticancer drug program. Assistant Secretary for Health, Edward Brandt, will testify; FDA Commissioner Arthur Hayes; Dr. Vincent DeVita, Director of the NCI; the Executive Director of the President's Commission on Ethics in Medicine and Biomedical and Behavioral Research, Alexander Capron; Dr. Charles LeMaitre, president of the M. D. Anderson Cancer Institute, and Dr. Charles Mortell, who is President of the Mayo Clinic and was also chairman of the Community Commission on Oncology and Technology Transfer, which committee was set up as a result of our last hearings when it was decided we needed to transfer the technology to those who were treating the patients.

So we will look forward to seeing as much interest in this hearing on Friday as we have had today. Thank you.

[Whereupon, at 3:35 p.m., the subcommittee was adjourned, to reconvene Friday, November 6, 1981, at 9:00 o'clock a.m.].

OVERSIGHT OF THE NATIONAL CANCER INSTITUTE, 1981

FRIDAY, NOVEMBER 6, 1981

U.S. Senate,
Committee on Labor and Human Resources,
Subcommittee on Investigations and General Oversight,
Washington, D.C.

The subcommittee met, pursuant to recess, at 9:03 a.m., in room 4232, Dirksen Senate Office Building, Senator Paula Hawkins (chairman of the subcommittee) presiding.

Present: Senator Kennedy.

Staff present: Jay Howell, chief counsel; James F. Michie, chief investigator; Terri Parker, counsel; and Tim Jenkins, investigator, for the majority staff; and Walter Sheridan and Larry Horowitz, minority professional staff.

Opening Statement of Senator Hawkins

Senator Hawkins. Good morning. We will come to order.

This subcommittee's major responsibility today is to help restore confidence in the National Cancer Institute. I want to begin by saying that I am just as convinced now, as I was prior to the subcommittee's hearing this past Tuesday, that the NCI's drug development program is needed and must be continued but with proper leadership. And, again, I think it is important for us to reassure the thousands of cancer patients now in treatment that there is cause for hope and they should continue to trust in the care of their doctors if their doctors know all the facts.

The purpose of these hearings is to rid the NCI and its regulator, the FDA, of some very serious program deficiencies. On Tuesday, I referred to these shocking deficiencies as the cancers of inaction, confusion, indecision, frustration, delay, and failure to communicate. Indeed, after the testimony on Tuesday, I was convinced that the NCI does not adequately protect patient safety. Management deficiencies that for years have crippled the programs of the NCI and its regulator, the FDA, must be immediately eliminated. The testimony I heard Tuesday and at every hearing we have held on this subject this year is evidence to the world that there is critical need for better management at NCI.

The testimony of Dr. Hensley revealed that, one, had it not been for the mother of a young cancer patient in Medford, Mass., writing a letter to the FDA, the FDA might never have learned of the misuse of the drug methyl-CCNU that resulted in severe and fatal kidney damage to patients.

Two, although toxicity data from animal studies conducted in the early 1970's warned of the potential for methyl-CCNU to cause kidney damage, clinicians were not advised.

Three, when the NCI did learn of this drug's life-threatening effects in humans, the NCI did not promptly inform the FDA and all of its clinical investigators.

Four, management of the FDA's Bureau of Drugs refused to vigorously pursue an investigation of the methyl-CCNU affair. And, once begun, the methyl-CCNU investigation was never completed.

In testimony concerning the drug DHAD, Dr. Hensley pointed out that warning of the life-threatening cardiotoxic effect of this drug was stated clearly in only two of 33 protocols, or methods of treatment, in human study. Why? Because the clinical investigators apparently were not aware of animal studies in the NCI and FDA files that revealed this problem. In recent months, the NCI has received reports of more than 25 cases of DHAD-related congestive heart failure, including 5 deaths. The failure to communicate is clearly evidenced by a recent letter from a clinician to the NCI. In his report on the death of a patient, the clinician wrote, "We were not aware of the cardiotoxicity of DHAD." Who is to blame?

Dr. Hensley also testified, "I think the relationship right now between the NCI and FDA is strained; I think NCI probably has very little inclination to be regulated, and I think FDA, certainly FDA management, has very little inclination to regulate." Dr. Hensley further stated that the reason he so aggressively pursued methyl-CCNU and the reason he came forth with the information is that he believed that "NCI did not adequately protect human subjects." Who is to blame?

FDA Inspector Meade stated that "the files" at NCI are "so disorganized." In reference to his recent inspection at NCI he said, "Basically, we had to ask directly for everything we got, and repeatedly ask for it." Who is to blame?

Dr. Wood, one of the FDA's most experienced chemists, testified, "there is extraordinary pressure at the present time to compromise scientific reviews, to force people to delete deficiencies that are essential for the establishment of good drug quality. And I think we are going to lose our scientific staff at the FDA if this continues." Who is to blame?

Dr. Richman, a supervisory pharmacologist with the FDA for 17 years, reaffirmed his statement of several months ago that the NCI's new and abbreviated animal testing of drugs is "unsound and he is severely distressed by the necessity of having to implement it." Who is to blame?

Ms. Ripper, one of the FDA's consumer safety officers, testified that she believes most of the NCI's drug submissions on file at FDA have problems; matters of concern to both agencies commonly slip through the cracks. Who is to blame?

Dr. Bono, chief of the NCI's Investigational Drug Branch until January of this year, was asked about his memorandum of April 30, 1980.[1] That memo warned his superior, Dr. MacDonald, of the lack of compliance with FDA regulations in the misuse of NCI drugs, and he asked Dr. MacDonald for his assistance in making it widely known that such misuse of NCI drugs would result in serious action. Dr. Bono's testimony to the Subcommittee was that he had decided not to send a letter of warning to the NCI's clinical investigators. Instead, he felt the answer was that he should continue on with the policy of persuasion and education rather than to go to a policy of threat.

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[1] Memo April 30, 1980, from Bono to Associate Director, CTEP may be found on p. 4.

Dr. MacDonald testified that Dr. Bono's memo raised his sensitivity to the issue but that he did not want to cut off innovation in clinical investigations. According to Dr. MacDonald, he suggested to Dr. Bono that the NCI's drug monitors remind the clinical investigators, as the monitors spoke with them on the telephone, that the misuse of drugs was not to be done. But there was nothing in writing.

Dr. Bono testified that he could not explicitly remember a discussion with Dr. MacDonald about this. Who is to blame?

Dr. Hoth of the NCI acknowledged that the drug development program still does not know the identities of all of the clinical investigators involved in the conduct of NCI-sponsored clinical trials. When asked about the NCI's failure to submit to the FDA animal data indicating the danger of heart damage from the drug DHAD, Dr. Hoth testified that, due to an internal administrative lapse, the study that was done in the fall of 1980 did not reach his attention until June of 1981.

Dr. Hoth also mentioned that program development has been an evolving process.

The evidence shows all too clearly that many of the problems in the NCI's program have nothing whatsoever to do with evolution. Rather, the program has been confused and disorganized and was painfully slow to react.

Either you promptly report life-threatening drug reactions or you do not. Either you submit to the FDA, and adequately consider, life-threatening potentials or you do not. Either you adequately monitor clinical trials or you do not. Either you give clear warning to clinicians who misuse anticancer drugs or you do not. Either you strictly account for drug supplies to prohibit diversion to illegitimate studies or you do not. Either you obtain adequate informed consent from patients who volunteer themselves for experimental use or you do not.

Either you perform FDA-NCI approved clinical trials, or you rely upon your own designs. Either you fully cooperate with a sister agency charged with overseeing your program or you do not. And either you tell the patients the truth or you do not.

With regard to the FDA as regulator of the NCI, two issues from Tuesday's hearing stand out very clearly in my mind as I reflect upon that long day. The first involves the FDA's two-paragraph response in June of this year to Mr. Palmadessa, a concerned father who had sought information on the treatment of his 8-year-old son. His son had died due to kidney failure caused by his treatment with the drug methyl-CCNU. Incredibly, the FDA sent the Palmadessas one of its boiler-plate brochures entitled Clinical Testing for Safe and Effective Drugs.[2]

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[2] Brochure "Clinical Testing For Safe and Effective Drugs" may be found on p. 40.

The second issue is the FDA's failure to aggressively pursue the investigation of the NCI's handling and reporting of injuries and deaths caused by the use of methyl-CCNU. It was only Tuesday of this week that we learned of Dr. Hensley's referral of that case to the Inspector General for HHS in October of 1980. What did the Inspector General do with this case? We were told that, for lack of resources, only one person was interviewed in March of 1981. We know that, following that one interview, nothing more was done with that case.

These issues and program failures paint a very bleak picture. There has been some progress, however, and we will hear about these efforts from Dr. Edward Brandt, Jr., Assistant Secretary for Health; Dr. Arthur Hull Hayes, Commissioner of the FDA; and Dr. Vincent DeVita, Director of the NCI.

Our other witnesses today include Mr. Alexander Capron, Executive Director of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, accompanied by his Deputy, Ms. Barbara Mishkin. Also appearing today, we have Dr. Charles LeMaistre, president of the University of Texas System Cancer Center, and Dr. Charles Moertel, director of the Mayo Comprehensive Cancer Center.

Senator Kennedy?

OPENING STATEMENT OF SENATOR KENNEDY

Senator KENNEDY. Thank you very much, Madam Chairman. I want to welcome our panel here this morning and welcome Dr. Hayes. I have not had the opportunity to hear Dr. Hayes as yet. He chairs an extremely important agency, one which this committee over a period of years has worked with. I welcome him to the committee this morning.

I do not think any of us here on this committee should minimize the problems that have been identified during the course of these hearings. They are serious. They are important. I believe they are basically administrative and they have to be remedied.

Madam Chairman, this committee can be sure of my complete and whole-hearted cooperation as we work through with the appropriate agencies to see the troublesome areas responded to effectively, efficiently and responsibly.

Having said that, I think it is extremely important that we also understand that the National Cancer Institute is not an agency in crisis. I think it is important that the American people understand that. There have been some administrative problems, but it is not an agency that is in crisis. That agency over a period of years has done more to preserve and enhance life, than any other agency in the Federal Government. And it continues to do so today with some of the most talented, skillful and compassionate people that have ever worked in a governmental agency and been committed to the cause of medicine. I think that is important, for people to understand, particularly those who have been reading the series of newspaper articles which I think so distort and misrepresent the real situation and puts in very significant fear of the prospects of future cure of cancer for themselves, and their children and their loved ones

I do not think there is any public discussion or debate, certainly not in this committee; about the importance of informed consent. And I yield to no one in the Senate or in any Government agency about insuring that any individual who is going to be the subject of medical experimental procedures is going to be fully and adequately informed. Our health subcommittee was responsible for the development of the protection of human subjects panel and worked closely with that panel over a period of years. Having attended a number of the meetings myself; having worked closely with administrations in the development of the balanced personnel on that panel; I believe that the panel has represented the best in terms of science, and expression of the Judeo-Christian ethics, and has made a very substantial contribution.

So, we all realize—and there is no debate or discussion—that informed consent is something that we are all committed to. No debate about that. No debate at all about the importance of the reporting of adverse side-effects to the appropriate clinical investigators and the responsibility of the agencies that are involved to communicate that to other clinical investigators, and that information to be given the kind of evaluation which trained and skilled medical personnel and researchers must give it. No debate on that at all.

No question that there have been questions raised about whether that process and procedures have been adequately followed in specific instances. Certainly we must remedy the process and procedures to ensure that in the future they will be adequate and complied with.

We are not debating those issues of public policy. Those have already been debated and discussed. This country is committed to the concepts of informed consent, and the adequate reporting of adverse effects, and the importance of ensuring that such information is carefully evaluated and communicated to the appropriate individuals and agencies.

But I think it is important for parents and for children to realize that, if any person in this country has contacted cancer, there is no place in the world—no place in the world—where that individual will be treated better than in the United States of America, nowhere. I think parents ought to understand that. I think children ought to understand that. Loved ones ought to understand that. And that is true today. That is true today. It is true this minute in spite of problems that we have heard.

The final point that I want to mention is that we will remedy these administrative problems, with the good support and cooperation of the agencies that are involved; and we will as a committee that is charged with oversight of these agencies; follow those issues and continue to follow them. But, after all is said and done, after we eliminate the administrative bottlenecks, we have to realize that the treatment of cancer under the best of circumstances is painful, full of anguish, full of suffering, full of disappointments. And that is going to be the lot for anyone who has the unfortunate and tragic circumstances of contacting cancer. That is part of the reality. It is a tragic part of the reality, but it is a part of the reality under the best of circumstances. When we put all of the problems behind, it is going to be an extremely painful journey and one full of anguish. And we ought to recognize that as well. Whatever we do here in this hearing is not going to make that any easier.

I welcome our panel here today and thank them.

Senator HAWKINS. We have with us today, as I have previously announced, Dr. Edward M. Brandt, Assistant Secretary for Health, who has been in his job, I understand, since March of 1981. Is that accurate?

Dr. BRANDT. Yes.

Senator HAWKINS. He is accompanied by Dr. Hayes, Commissioner of the FDA, who has an appointment, I understand, at the White House this morning. Is that correct?

Dr. HAYES. Yes.

Senator HAWKINS. He is operating under time constraints. Dr. Vincent DeVita is Director of the National Cancer Institute. Dr. Crout is Director of the FDA's Bureau of Drugs.

We appreciate your joining us here today. Your testimony will be of great help to this subcommittee in its continuing review and evaluation of the national cancer program. Dr. Brandt, I believe you have a prepared statement for submission in the record. In the interest of saving time, could you summarize that statement? And then we will ask you maybe one question apiece and then go to Dr. Hayes so he can be excused to go to his White House appointment. We will come back to you. Dr. Brandt.

STATEMENT OF EDWARD N. BRANDT, JR., M.D., ASSISTANT SECRETARY FOR HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY ARTHUR HULL HAYES, COMMISSIONER, FOOD AND DRUG ADMINISTRATION; J. RICHARD CROUT, DIRECTOR, BUREAU OF DRUGS, FOOD AND DRUG ADMINISTRATION; AND VINCENT T. DEVITA, JR., DIRECTOR, NATIONAL CANCER INSTITUTE

Dr. BRANDT. Thank you very much, Madam Chairman. Madam Chairman and Senator Kennedy, I am Dr. Ed Brandt, Assistant Secretary for Health of the Department of Health and Human Services.

I and my colleagues are here today to discuss cancer and the search for effective treatments and possibly a cure. It is an emotional subject. It touches all of us, for the effects of cancer are devastating and often fatal.

We are here today to present objectively the complexities of cancer research and how agencies of this department sponsor and monitor this research.

I believe it necessary to address the issues involved in cancer therapeutic research in three ways:

First is the concept of risk assessment: How much risk in terms of toxicity should be tolerated in therapeutic research given the grave consequences of many forms of cancer?

Second, in the evaluation of new drugs for the treatment of cancer, how much regulation should be imposed on clinical trials so that the patient is protected without at the same time curbing innovative medical research?

Third, in determining the appropriateness of monitoring systems in cancer drug development and the regulation of such systems, are the efforts by the FDA and the NCI appropriate and sufficient given the nature of cancer drug development?

The programs of the National Cancer Institute to develop anticancer drugs were mandated by Congress in 1955. The wisdom of that mandate is evident. Anticancer drugs have increased our progress in the treatment of cancer. I would urge you to consider the following.

Up to 45 percent of patients with cancer can be cured today.

Fully half of the children with cancer, most patients with Hodgkin's disease and most young men with testicular cancer are cured today.

Progress is being made against major forms of cancer in adults as well. Breast cancer patients now receive drugs earlier in the treatment of their disease, and they are living longer.

Of the 355,000 patients with cancer who were curable in 1980, the NCI estimates that 46,000 were curable because drugs were used alone or in combination with radiation treatment or surgery.

Despite these successes, some 420,000 still die of the disease each year, and it is for these patients that we must continue to search for and develop better drugs.

The toxicity associated with the use of these powerful drugs is recognized by all those involved in this important research. The benefits that accrued are the successes we have made against certain forms of cancer. The risks of such research involving humans is minimized through the clinical trials system at NCI, the monitoring of that system by NCI, the regulation by the FDA, and through the regulation issues which require careful analysis of risks and benefits by individual institutional review boards.

It is important to emphasize that anticancer drugs are orphan drugs; their development is still not attractive to the pharmaceutical industry for a whole variety of reasons. Yet, because these drugs can cure some cancers, there is a demand for them by patients and their physicians long before new drugs are available commercially.

The first stage that a compound goes through is screening. This is the process of narrowing the vast number of chemicals that might be useful down to the few that can be tested in humans.

Another step before a drug begins clinical trials is toxicology testing for adverse effects in both mice and dogs. These tests are invaluable in assuring that the dose of the drug used in the initial human studies is safe, again, minimizing the risk.

The human studies proceed in a precise way through carefully phased trials. Phase I determines a drug's dose and safety with potential therapeutic benefit as the basic intent. Phase II determines whether a drug works. Phase III determines whether a new drug is better than the standard treatment for a particular form of cancer. Let me emphasize that therapeutic intent is ever present in all stages of clinical trials for cancer drugs including phase I.

A phase I study involves about a hundred cancer patients who have rapidly growing cancers, untreatable by standard means. Most of these patients have an average life expectancy of 6 months.

The underpinning of phase I trials, I again emphasize, is therapeutic intent. It is important to note that drug-related death is uncommon in phase I studies. During the past 18 months NCI reports indicate 3 percent of patients treated with phase I drugs died of drug-related causes.

Once a dose is established, the drug is put into phase II studies to test for tumor shrinkage or efficacy in specific tumor types. Again, patients who receive these drugs have exhausted all known treatments for their growing cancers.

Once a drug has demonstrated antitumor activity against a particular form of cancer, investigators proceed with the larger phase III. The main purpose of these studies is to discover new treatments that offer advances over our present ones.

Let me mention again that there is a lag between demonstration of effectiveness of an anticancer drug and preparation for marketing by a commercial interest. NCI, with the concurrence of the FDA, developed a drug distribution system in 1976 to help meet the needs of cancer patients to get access to a drug that is effective while at the same time restricting the distribution of drugs in early experimental phases.

For the clinical trials system to function properly and to ensure the safety of patients involved in these studies, it is important to understand the relationship between NCI and the FDA and their roles in monitoring and regulating the system.

I want to emphasize the evolving nature of this relationship as well as that of their individual systems of monitoring and regulation. Until the mid-1970s, the system operated with an administrative laxness in certain areas that both institutions came to recognize as inappropriate. Management in both NCI and FDA addressed these problems, the outcome of which has been the establishment in recent years of some special procedures between FDA and NCI with respect to cancer drugs.

Madam Chairman, before I discuss the various programs of the NCI and the FDA as well as the role of institutional review boards, let me discuss very briefly the relationship between medical research innovation and regulation. Indeed we must protect the rights and welfare of patients participating in research. Yet, we must also provide the scientific community with the flexibility to conduct innovative and therapeutic clinical trials. I believe that the monitoring and drug distribution efforts of the NCI, the regulatory monitoring functions of the FDA, and the important role playing by the institutional review boards at research institutions around the country provide a framework for scientific research that allows for innovation while protecting the patients.

We fully recognize that problems have arisen and still do exist. We are working to correct those as we have done in the past. We will continue to seek ways to improve the system.

The major components of the relationship between NCI and FDA and their evolving nature are as follows.

First, a memorandum of understanding between FDA and NCI was published in the Federal Register and became effective on February 5, 1979. Under this memorandum, NCI reaffirmed its policy of complying with all applicable laws, regulations, and any other legal requirements pertaining to sponsorship of new drugs and to transmit to FDA pertinent information generated by its activities.

The NCI drug master file: under the memorandum of understanding, the NCI maintains a drug master file at FDA which describes NCI's overall drug development system, its method of monitoring ongoing studies and of communicating new information on drug efficacy and adverse events to its own investigators and to FDA.

Drug distribution: By the early 1970's it became apparent to both FDA and NCI that the wide distribution policies for investigational anticancer drugs required change. As the number of drugs under test increased, the NCI proposed and the FDA approved a new plan that restricted distribution of investigational drugs into three groups. These groups are group A, which includes those drugs in phase I and early phase II studies. These studies were closely monitored by a contractor-operated clinical trials monitoring system. This monitoring system collects all of the data from the 10 phase I and early phase II contractors, site visits them regularly, and spot checks raw data.

Group B includes those drugs in later stages of phase II and in phase III studies. Distribution of these drugs is limited to investigators participating in the cooperative groups and cancer centers as well as to our contract-supported investigators. Monitoring of studies conducted by cooperative groups is currently delegated to the central management of those groups with NCI supervision.

NCI, however, will soon begin testing of a contract system of periodic site visits to clinical investigators using group B drugs.

Group C are those drugs that show a clear and consistent pattern of efficacy for a particular form of cancer. Drugs enter into this category by mutual agreement of NCI and FDA.

With an increasing number of well-trained specialists and medical oncology entering private practice in the United States, the NCI is planning to establish a large network of community clinical oncology programs. This program addresses some of the concerns developed out of hearings held by this subcommittee last spring.

Those monitoring arrangements meet FDA's current regulations, and FDA has approved NCI's drug distribution and monitoring system as described in its master file.

One problem which we believe will be addressed by the improving drug distribution system is that of leakage. Leakage is a term used by industry that refers to the leaking of unused amounts of an investigational drug that may not be returned to the sponsor as required and are instead possibly used to treat other patients. We recognize the seriousness of this problem and are taking the steps outlined above as well as instituting a new drug accountability system.

Another area of evolving improvement in NCI and FDA systems is toxicology testing. A recent addition to the master drug file is a toxicology protocol that relies primarily on the mouse and dog to establish major organ toxicity and a starting dose for human studies. The new system was reviewed and approved by both NCI and FDA and, I would emphasize, external advisors.

I would point out that all phase I trials are intended to evaluate toxicity as well as potential benefit so that side effects are common in such studies. The key to minimizing risks in these studies is careful monitoring of the patients who participate, not the conduct of unnecessary preclinical toxicology studies in animals.

In order to understand present efforts to provide adequate protection for human subjects involved in research, it is necessary to review the history of the development of policy in this area.

During the period 1974 to 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research carried out extensive evaluation of the then HEW policy and procedures for the protection of human subjects. In general, the National Commission found that the Department's procedures constitute a sound and appropriate structure for protecting human subjects while allowing institutions to carry out scientific research without inappropriate government intrusion.

The Department published proposed rules for the protection of human subjects in August 1979. In addition, the Department considered and adopted nearly all of the recommendations of the National Commission and those of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. The new regulations were published in January 1981.

Since these regulations were put in effect in July of 1981, the Department has established certain mechanisms to provide evidence that IRBs are meeting their responsibilities. For each research project covered under these regulations, the institutional review board must certify that the project meets the Department's standards.

The Public Health Service has instructed peer review groups to make a second evaluation of research proposals.

If problems of noncompliance with the regulations are brought to the attention of the Office of Protection from Research Risks from any source, they are promptly investigated.

Additional mechanisms are under consideration. These include development of a system whereby consent documents approved by IRBs will be randomly selected and reviewed.

As part of the overall IRB monitoring effort, FDA in 1977 began an expanded program of IRB inspections. Information of an adverse nature is shared with the Office of Protection from Research Risks which has oversight responsibility for our regulations. FDA's new regulations as well as the Department's human subjects regulations do provide for administrative actions that can be applied in instances of noncompliance.

Although in the final analysis the best protection for human subjects involved in research rests on the research investigator, we recognize our responsibility to effectively regulate and monitor IRB performance. Consequently, the NIH and the FDA have entered jointly into an education program. We believe that this program is the most effective way to provide sensitive application of sound ethical principles to the preservation of the rights and welfare of human subjects.

Let me turn briefly to the issue of informed consent. It is an issue that involves the cancer patient, his or her physician, the NCI, the FDA, and the NIH. After a protocol for a study involving an investigational drug is developed, it is reviewed for merit and safety at the investigator's institution. That IRB approves the protocol and the informed consent form submitted by the investigator. The package is then sent to NCI, where it undergoes several further reviews.

The new regulations require the IRB, where appropriate, to make certain that there are adequate provisions for monitoring the data collected to insure the safety of subjects and to see that each subject is informed of significant new findings developed during the course of the research which may relate to that subject's willingness to continue participation.

Yet, this review process or any other review process cannot answer the question: Is the information presented to the patient in such a way that he or she can make an intelligent choice? The answer ultimately depends on how effective the discussions are between the patient and their physician. After all, informed consent is more of a process than the signing of a form. It is, in fact, a continuous process that must start with full and careful explanation by a physician and the signing of a document by a patient, but it continues on a daily basis as the patient interacts with their physician and other health professionals.

Madam Chairman, it is clear from the many changes ongoing in the systems of NCI and FDA that progress toward more appropriately managed and controlled clinical investigations is being made. I believe further improvements are possible. As you know, and certainly partly in response to your concerns, I have appointed a task force to review the investigational new drug program of NCI and its regulation by FDA.

The mission of that task force is broad. It will review not only the management structure and policies of the FDA and NCI but also how the drug distribution and monitoring systems respond to management. You can be assured that I will share with you the results and recommendations as soon as I receive them.

In closing, let me reiterate what I believe must be the essential starting point for any discussion or assessment of the drug development programs of the NCI.

It is important to continually emphasize the fact that we are talking about a program that is unique to American medical science. This system of cooperative drug development brings the collective talents and expertise of scientists, clinical researchers, and practicing physicians from universities, clinical centers, community hospitals, the staffs of the NCI and the FDA as well as involving all of us within the Public Health Service who take as our mission the protection, assurance, and advancement of the health of the American public. In addition, the success of our efforts depends upon thousands of individuals, cancer patients, their family, their friends, who make tremendous personal contributions and at times sacrifices to aid in improving our knowledge. All of these collective efforts are focused on addressing the critical issues presented by one of this Nation's greatest health problems, cancer.

As our experiences enhance our knowledge and understanding, the system can and will be further corrected and further improved. But, although you and I would be foolish not to recognize that there are and have been difficulties and weaknesses in this program, we would be even more foolish not to recognize the fact that our ability to perceive and ultimately correct these problems is dependent to a certain degree on the luxury of hindsight. It is only through the process of working with this drug development system that we ever reach the position of being able to look backward and discover new ways to develop new drugs more safely, more effectively and perhaps more humanely in the future.

I look forward to continuing to work with all who are concerned as we seek improvements in our present system as diligently but also as constructively as possible.

Madam Chairman, this concludes my statement. We will be happy to respond to questions from you and members of the subcommittee.

Senator HAWKINS. Dr. Brandt, you referred to the letter that I wrote to Secretary Schweiker on July 9, 1981 advising him of the specific incidents of adverse drug reactions in NCI sponsored clinical trials. In response to that letter Secretary Schweiker had established under your direction a special task force which you referred to in examining the NCI sponsored clinical trials. Could you give us a progress report on that?

[The prepared statement of Mr. Brandt and information referred to follow:]

STATEMENT
BY
EDWARD N. BRANDT, JR., M.D.
ASSISTANT SECRETARY FOR HEALTH
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Madame Chairman and Members of the Subcommittee:

I am Edward N. Brandt, Jr., M.D., Assistant Secretary for Health, Department of Health and Human Services. With me today are Vincent DeVita, M.D., Director of the National Cancer Institute and Arthur Hull Hayes, M.D., Commissioner, Food and Drug Administration. We are here today to discuss cancer and the search for effective treatments and possibly a cure. It is an emotional subject that touches all of us for the effects of cancer are devastating and often fatal. We are here today, however, to present objectively the complexities of cancer research and how agencies of the Department sponsor and monitor this research.

I believe it necessary to address the issues involved in cancer research in three ways:

- First, the concept of risk assessment -- how much risk in terms of toxicity, should be tolerated in therapeutic research given the grave consequences of many forms of cancer?

- Second, in evaluating new drugs -- how much regulation should be imposed on clinical trials so that the patient is protected without curbing innovative medical research?

- Third, in determining the appropriateness of monitoring systems in cancer drug development and the regulation of such systems -- Are the efforts by the FDA and the NCI appropriate and sufficient given the nature of cancer drug development?

The programs of the National Cancer Institute to develop anticancer drugs were mandated by Congress in 1955. The wisdom of that mandate is evident now, nearly 30 years later. Anticancer drugs have increased progress in treating cancer:

- Up to 45 percent of patients with cancer can be cured today. That is a great improvement compared to 30 years ago when only 33 percent were cured. This increased cure rate is due in part to improvements in surgery and radiation therapy, but also to the dramatic growth of drug treatment.

- Fully half of children with cancer, most patients with Hodgkin's disease and most young men with testicular cancer are cured today. Drug treatments contributed to these advances which are now mirrored in our national statistics; we see a decrease in mortality nationwide for these diseases and a sharp decrease in cancer mortality for Americans under the age of 45.

- Progress is being made against major forms of cancer in adults as well. Breast cancer pateints now receive drugs earlier in the treatment of their disease, and they are living longer. In fact, survival has increased for seven of the 10 major forms of cancer in white Americans and six of the 10 in blacks.

- Of the 355,000 patients with cancer who were curable in 1980, NCI estimates 46,000 were curable because drugs were used alone or in combination with radiation treatment or surgery. This sizable benefit must always be considered when discussing the risk of treatment with anticancer or any other potent drug.

Despite these successes, some 420,000 still die of the disease each year, and it is precisely for these patients that we must continue to search for and develop better drugs. For while surgery and radiation therapy can be used to successfully treat localized cancer, drugs are currently our only weapon against cancer cells that circulate in the bloodstream and spread to other organs.

The toxicity associated with the use of these powerful drugs is recognized by all those involved in this important research. The benefits that have accrued are the successes we have made against certain forms of cancer. The risks of such research involving humans is minimized through the clinical trials system at NCI, the monitoring of that system by NCI, regulation by FDA, and through the regulation issued which require careful analysis of risks and benefits by Institutional Review Boards.

The Clinical Trials System

Anticancer drugs are orphan drugs, their development is still not attractive to the pharmaceutical industry for several reasons. Together, all anticancer drugs are used in the treatment of less than 200,000 patients per year, and an individual drug is used in the treatment of even fewer patients. Yet because these drugs can cure some cancers, there is a demand for them by patients and their physicians long before new drugs are available commercially.

The NCI's Drug Development Program participated in the development of all 21 anticancer drugs that have become commercially available since the program began in 1955. This list includes drugs such as Cisplatin, Adriamycian and Bleomycin that have had a major impact on the treatment of cancer. NCI currently sponsors IND's (investigational new drug application) on 86 drugs, and in 1980 more than 32,000 cancer patients entered NCI-sponsored chemotherapy trials, many of them benefitting from the earliest phase of experimental treatment.

The first stage a compound goes through is screening. This is the process of narrowing the vast number of chemical that might be useful down to the few that can be tested in humans. Every year, NCI evaluates about 15,000 natural and synthetic chemicals in mice with cancer. These compounds are selected from many more suggested by universities, research institutions, pharmaceutical and chemical industries worldwide, NCI's own intramural laboratories, and other government agencies. Compounds that show activity in this first level of screening are presented to a group of 30 NCI staff. This group called the Decision Network Committee, meets every two months. It uses precise criteria to decide whether a drug can advance from one stage of testing to the next.

Another step before a drug begins clinical trial is toxicology testing for adverse effects in mice and dogs. These tests are invaluable in assuring that the dose of the drug used in the initial human studies is safe -- again, minimizing the risk. The studies also look at damage to various organs to predict what side effects might be encountered. We already know anticancer drugs damage dividing cells and can produce unpredictable toxicity. Because no animal or test tube system is absolutely correct in predicting toxic effects of any drug, the investigator monitors each patient for all possible toxicity. Early human studies are monitored very carefully to search for unpredictable side effects. Before human studies can begin, an application called an IND must be prepared for submission to the FDA. The IND includes all animal data on safety and efficacy. After FDA reviews and approves the IND, human studies begin. Only one out of every 5,000 compounds put into the system gets to this stage. The human studies proceed in a precise way through carefully phased trials: Phase I determines a drug's dose and safety with potential therapeutic benefit as the basic intent; Phase II determines whether a drug works; Phase III determines whether a new drug is better than the standard treatment for a particular form of cancer. I would emphasize that therapeutic intent is ever present in all stages of clinical trials for cancer drugs be it Phase I, II, or III.

A Phase I study involves about 100 cancer patients who have rapidly growing cancers, untreatable by standard means. Most of these patients have an average life expectancy of six months. Phase I testing of anticancer drugs differs in an important way from that of drugs for other diseases. Instead of being conducted on normal subjects as is the practice for other drugs, Phase I studies on anticancer drugs, for ethical reasons, are conducted in the very population for whom the treatment is ultimately intended. Therefore, a patient treated in a Phase I study of anticancer drugs has a prospect of therapeutic benefit. Again, I want to emphasize that the underpinning of Phase I trials is therapeutic intent. It is important to note that drug-related death is uncommon in Phase I studies. During the past 18 months NCI reports indicate thre percent (43 of 1,471) patients treated with Phase I drugs died of true drug-related causes. The antitumor response rate in Phase I trials exceeds this figure.

Once a dose is established, the drug is put into Phase II studies to test for tumor shrinkage or efficacy in specific tumor types known as the clinical panel. Again, patients who receive these drugs also have exhausted all known treatments for their growing cancers. A question often asked is at what point is an experimental drug considered ineffective or too toxic and withdrawn from human experiments. With only two doses and two schedules in 30 patients for each of eight tumor types, about 1,000 patients are required to complete a minimal Phase II test. The failure to complete a test can be tragic if a useful drug is passed over. For example, methyl GAG, a drug that studies suggest will be of significant value in treating patients with lymphomas, was almost discarded because it was initially tested in too few patients on too few schedules -- again establishing the careful balance between benefit and risk of toxicity.

Once a drug has demonstrated antitumor activity against a particular form of cancer, investigators proceed with the larger Phase III. The main purpose of these studies is to discover new treatments that offer advances over our present ones.

I would like to mention again that there is a lag between demonstration of effectiveness of an anticancer drug and preparation for marketing by a commercial interest. Because drugs have shown effectiveness, there is a demand for them. NCI, with the concurrence of the FDA, developed a drug distribution system in 1976 to help meet the needs of cancer patients to get access to a drug that is effective while at the same time restricting the distribution of drugs in early experimental phases. I will discuss that system in a minute.

Relationship Between NCI and FDA

As the Assistant Secretary for Health, I am responsible for ensuring that the Public Health Service, which includes the NCI and the FDA, is properly managed and effective in its mission. I recognize that the programs of the NCI and the FDA have been evolving over the past decade, particularly in terms of progressively improving the clincal trials system. That improvement will continue. In addition, the NCI has invested considerable effort in recent years in updating its monitoring and drug distribution systems. The FDA has also extensively reviewed its regulatory efforts with respect to cancer drugs.

For the clinical trials system to function properly and to ensure the safety of patients involved in these studies, it is important to understand the relationship between NCI and the FDA and their roles in monitoring and regulating the system.

I want to emphasize the evolving nature of this relationship as well as that of their individual systems of monitoring and regulation. Until the mid-1970's, the system operated with an administrative laxness in certain areas that both institutions came to recognize as inappropriate. For example, prior to 1974, NCI IND's often did not contain sufficiently detailed information to permit FDA reviewers to make an independent judgement on the safety of the proposed studies, annual progress reports were overdue so that FDA could not follow the progress of the studies, many INDs's were listed as still active when clinical investigations had long been terminated, and the distribution of investigational cancer drugs demonstrated to be effective but not yet marketed to practitioners was relatively uncontrolled. Prior to this time physicians had to file individual compassionate IND's with FDA even thought NCI was the supplier of the drug. This created a burden on FDA staff and slowed the access to anticancer agents considerably. Management in both NCI and FDA addressed these problems, the outcome of which has been the establishment in recent years of some special procedures between FDA and NCI with respect to cancer drugs.

Madame Chairman, before I discuss the various programs of the NCI and the FDA as well as the role of Institutional Review Boards (IRB's), I want to discuss very briefly the relationship between medical research innovation and regulation. Indeed we must protect the rights and welfare of patients participating in research and yet also provide the scientific community with the flexibility to conduct innovative and therapeutic clinical trials. As I said in testimony last week on this subject, there is a fine line between permitting freedom for innovation and the monitoring by sponsors and regulation by government agencies. The FDA is often accused of too much regulation and thus curbing research. Others accuse the FDA of not regulating the investigators closely enough. We realize that the fine line we must follow has a potential for overregulating or for allowing too much freedom for investigators. But as a system, I believe that the monitoring and drug distribution efforts of the NCI, the regulatory monitoring functions of the FDA, and the important role played by IRB's at research institutions around the country provide a framework for scientific research that allows for innovation while protecting the patients. We fully recognize that problems have arisen and still do exist. We are working to correct those as we have done in the past. We will continue to seek ways to improve the system.

The major components of the relationship between NCI and FDA and their evolving nature are as follows:

- Memorandum of Understanding - A memorandum of understanding (MOU) between FDA and NCI was published in the *Federal Register* and became effective on February 5, 1979. Under this MOU, NCI reaffirmed its policy of complying with all applicable laws, regulations, and any other legal requirements pertaining to sponsorship of new drugs and to transmit to FDA pertinent information generated by its activities. Both parties are committed to maintaining lines of communication with each other in order to exchange information and to resolve differences.

- NCI Drug Master File - Under the MOU, NCI maintains a Drug Master File at FDA which describes NCI's overall drug development system, its method of monitoring ongoing studies and of communicating new information on drug efficacy and adverse events to its own investigators and to FDA. The master file also lists the clinical investigators who conduct early human trials of cancer drugs, their qualifications, and the facilities in which they works. Drug master files are a common device used by FDA to reduce the need for repetitive submission of information. Drug master files from drug firms, however, almost entirely contain chemistry information on such matters as synthetic processes, formulations, and manufacturing facilities. NCI is the only sponsor that develops a sufficient number of drugs in a single areas in a repetitive manner that it has found it useful to submit a drug master file on its development and monitoring procedures. There is no policy obstacle to any drug firm doing the same if it wishes.

- Drug Distribution - By the early 1970's it became apparent to both FDA and NCI that the wide distribution policies for investigational anticancer drugs required change. As the number of drugs under test increased, the NCI proposed and FDA approved a new plan that restricted distribution of investigational drugs into three groups. The key to the success of this plan was a provision for FDA and

NCI to make effective drugs available to cancer patients in the premarketing phase. These groups are defined as follows:

> Group A - includes those drugs in Phase I and early Phase II studies. Their distribution is now limited to physicians at institutions under contract with the NCI to conduct these early studies. Group A studies are closely monitored for NCI by a contractor-operated Clinical Trials Monitoring System (CTMS). The CTMS collects all the data from the 10 Phase I and early Phase II contractors, site visits them regularly, and spot checks raw data. Group A investigators meet three times a year with NCI staff and review all data on each drug.
>
> Group B - includes those drugs in later stages of Phase II and in Phase III studies. Distribution of these drugs is limited to investigators participating in the NCI-funded cooperative groups and cancer centers as well as to our contract-supported investigators. Monitoring of studies conducted by cooperative groups is currently delegated to the central management of those groups with NCI supervision.

NCI will soon being testing a contract system of periodic site visits to clinical investigators using Group B drugs. This will be a system similar to the CTMS used for Group A drugs.

- Group C - drugs that show a clear and consistent pattern of efficacy for a particular form of cancer. Drugs enter into this category by mutual agreement between NCI and FDA. They are made available to physicians who register with the NCI and agree to use the drug for the stated indication. Investigators must agree to report to NCI any adverse drug reactions associated with these drugs and NCI is responsible for then reporting them to FDA.

With an increasing number of well-trained specialists in medical oncology entering private practice in the US, NCI is planning to establish a large national network of community clinical oncology programs. This program addresses some of the concerns developed out of hearings held by the Chairman last spring. NCI ultimately hopes to be able to restrict distribution of Group C investigational drugs to physicians who participate in this and other official NCI programs thus further improving the monitoring of these drugs.

These monitoring arrangements meet FDA's current regulations, and FDA has approved NCI's drug distribution and monitoring system as described in its Drug Master File.

One problem which we believe will be addressed by the improving drug distribution system is that of leakage. Leakage is a term used by industry that refers to the leaking of unused amounts of an investigational drug that may not be returned to the sponsor as required and are instead possibly used to treat other patients. We recognize the seriousness of this problem and are taking the steps outlined above as well as instituting a new drug accountability system. This system which will be piloted this year calls for a vial-by-vial accounting by investigators.

o Toxicology Testing - Another area of evolving improvement in NCI and FDA systems is toxicology testing. A recent addition to the Master Drug File is a toxicology protocol that relies primarily on the mouse and dog to establish major organ toxicity and a starting dose for human studies. The new system was reviewed and approved by both NCI and FDA external advisors.

It is based on studies by NCI investigators showing that of 120 major toxicities, the monkey predicted in only two instances a toxic reaction not shown in the dog. In several cases the monkey falsely predicted toxicities never seen in man. Additional studies showed that the mouse correctly predicted safe strating doses for all 19 drugs evaluated to date. This new toxicology protocol is intended to facilitate entry of cancer drugs into Phase I trials without materially increasing the risks of these trials and not compromising a patient's safety. I would point out that all Phase I trials are intended to evaluate toxicity as well as potential benefit, so that side effects are common in such studies. The key to minimizing risks in such studies is careful monitoring of the patients who participate, not the conduct of unnecessarily preclinical toxicology studies in animals. Use of these new guidelines is not limited to NCI. Any other medical institution or drug firm can use them, provided the clinical research is done in cancer centers staffed and equipped to monitor patients carefully.

- Meetings Between FDA and NCI - Under the MOU, representatives of FDA and NCI at both staff and management level meet periodically to discuss problems of mutual concern. These meetings are intended to increase mutual understanding and to deal with general matters such as the Drug Master File. These meetings are beneficial to both agencies and I expect them to continue. Although more meetings of this type are held with NCI, the system is not unique at FDA in regard to other sponsors.

Institutional Review Boards and Informed Consent

In order to understand present efforts to provide adequate protection for human subjects involved in research, it is necessary to review the history of the development of policy in this area.

During the years 1974-1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research carried out extensive evaluation of the then HEW policy and procedures for the protection of human subjects. Although the National Commission issued many reports, the final and most important report of the Commission concerned the Department's system of using IRB's as the centerpiece of a comprehensive system for protecting human research subjects. In general the National Commission found that the Department's procedures constitute a sound and appropriate structure for protecting human subjects while allowing institutions to carry out science without inappropriate government intrusion.

The principal thrust of the recommendations of the National Commission was in the direction of prior review of research in order to prevent intrusion upon the rights and welfare of human subjects involved in research. The Department published proposed rules for the protection of human subjects in August, 1979 in coordination with a parallel effort with the FDA. In addition, the Department considered and adopted nearly all of the recommendations of the National Commission and those of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. The new regulations were published in January, 1981.

Three long-established principles were recommended by the National Commissiona and adopted by the Department:

- All research involving humans must be carried out in a manner that includes respect for persons;
- Only research expected to produce greater good than harm is to be permitted;
- In the evaluation of research, principles of justice must govern.

These principles are embodied in the provisions of the regulations which require informed consent, a favorable risk-benefit ratio, and equity in the selection of subjects. Since the regulations were put in effect in July, 1981, the Department has established certain mechanisms to provide evidence that IRB's are meeting their responsibilities.

- For each research project which is covered under the human subject regulations, the IRB must certify that the project meets the Department's standards.
- The Public Health Service has instructed peer review groups to make a second evaluation of research proposals in order to make certain that subjects are adequately protected.
- If problems of noncompliance with the regulations are brought to the attention of the OPRR from any source they are promptly investigated.
- Additional mechanisms are under consideration. These include development of a system whereby consent documents approved by IRB's will be randomly selected and reviewed. Should any consent documents fail to

> meet the requirements of the regulations, corrective action will be taken. Serious deficiencies may lead to withdrawal of the institutional assurances which must be in place to permit the institution to qualify for Department funding. Also under consideration is a plan to initiate regular site visits to awardee institutions to assess the adequacy of human subject protections.

As part of the overall IRB monitoring effort, FDA, in 1977, began an expanded program of IRB inspections. Currently FDA conducts approximately 400 such inspections annually. The Bureau of Drugs, specifically, currently inspects some 200 such IRB's a year. Following each inspection, a letter is sent to the IRB summarizing the results, identifying areas where improvement should be made and offering guidance. Information of an adverse nature is shared with the Office of Protection from Research Risks (OPRR) which has oversight responsibility for HHS human subjects regulations. FDA's new IRB regulations as well as the Department's human subjects regulations, do provide for various administrative actions that can be applied in instances of non-compliance. These may be directed at the IRB's or their parent institutions. These sanctions range from reinspection to disqualification of the parent institution or the IRB. A recent evaluation of 110 IRB's shows that we have additional work to do to improve their performance. Although few serious deficiencies were found, 37 out of the 110 IRB's were deficient to some degree but only three were of a serious nature.

Although in the final analysis, the best protection for human subjects involved in research rests on the research investigator, we recognize our responsibility to effectively regulate and monitor IRB performance. Consequently, the NIH and FDA have entered jointly into an education program. We believe that this program is the most effective way to provide sensitive application of sound ethical principles to the preservation of the rights and welfare of human subjects. I further believe that the combination of written assurances, quality checks, sampling of consent documents, routine site visits, and education will provide a comprehensive program which will be effective.

I would like to turn briefly to the issue of informed consent. It is an issue that involves the cancer patient, his or her physician, the NCI, the FDA, and the NIH. After a protocol for a study involving an investigational drug is developed, it is reviewed for merit and safety and the investigator's institution. This IRB approves the protocol and the informed consent form submitted by the investigator. The package is sent to NCI where it undergoes several further reviews.

The new regulations require the IRB, where appropriate, to make certain that there are adequate provisions for monitoring the data collected to insure the safety of subjects, and to see that each subject is informed of significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation.

Yet this review process cannot answer the question: Is the information presented to the patient in such a way that he/she can make an intelligent choice? The answer ultimately depends on how effective the discussions are between the patient and physician. After all, informed consent is more of a process than the signing of a form. Because patients are ill and therefore under a great deal of stress, their anxiety may impair their ability to comprehend difficult medical information and to make a sound judgement. This may call for repeated conversations, explanations and depends on the skill of the physician and how he/she interacts with the patient.

Informed consent is therefore a continuous process that starts with a full and careful explanation by a physician and the signing of a document by a patient, but continues on a daily basis as the patient interacts with the doctor and other health professionals involved in the case. Our educational efforts, improved monitoring and regulatory efforts are moving us toward a better understanding by investigators of their responsibilites to patients.

Task Force to Review the IND Process

Madame Chairman, it is clear from the many changes on-going in the systems of NCI and FDA, that progress toward more appropriately managed and controlled clinical investigations is being made. However, I believe further improvements are possible. As you know, and certainly partly in response to your concerns, I have appointed a task force to review the investigational new drug program of NCI and its regulation by FDA.

The mission of that task force is broad. It will review not only the management structure and polices of the FDA and NCI but also how the drug distribution and monitoring systems respond to management. The task force will report its findings and recommendations to me by the end of this year. I am confident that this review will be objective and beneficial to both the clinical trials sponsored and monitored by NCI and the regulation of this process by FDA. You can be assured that I will share with you the results and recommendations as soon as I receive them.

In closing, I think it is important to reiterate what I believe must always be the essential starting point for any discussion or assessment of the drug development programs of the NCI.

It is important to continually emphasize the fact that we are talking about a program unique to American medical science. This system of cooperative drug development brings the collective talents and expertise of scientists, clinical researchers, and practicing physicians from universities, clinical centers, community hospitals, the staffs of the NCI and the FDA, as well as involving all of us within the Public Health Service who take as our mission the protection, assurance, and advancement of the health of the American public. In addition, the success of our efforts depends on thousands of individuals, cancer patients, their family and friends -- who make tremendous personal contributions and at times sacrifices to aid in improving our knowledge. All of these collective efforts are focused on addressing the critical issues presented by one of this nation's greatest health problems -- cancer.

By its very nature -- because it si an unprecedented endeavor, because it has no previous model to follow in American medical science -- it is and must be an evolving system; one in which we are constantly attempting to refine our knowledge and to make improvements in our methods. In this respect, it shares a fundamental similarity to all major research efforts and scientific developments. As our experiences enhances our knowledge and understanding, the system can and will be further corrected and further improved. But although you and I would be foolish not to recognize that there are and have been difficulties and weaknesses in this program, we would be even more foolish not to recognize the fact that our ability to perceive and ultimately correct these problems is dependent to a certain degree on the luxury of hindsight. It is only through the process of working with this drug development system that we ever reach the luxurious positon of being able to look backwards and discover new ways to develop new drugs more safely, more effectively and perhaps more humanely in the future.

I look forward to continuing to work with all who are concerned that we seek improvements in our present system as diligently but also as constructively as possible.

Madame Chairman, this concludes my statement. We will be happy to respond to questions from you and Members of the Subcommittee.

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United States Senate

COMMITTEE ON LABOR AND
HUMAN RESOURCES
SUBCOMMITTEE ON INVESTIGATIONS
AND GENERAL OVERSIGHT
WASHINGTON, D.C. 20510

July 9, 1981

The Honorable Richard S. Schweiker
Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Secretary:

As we agreed yesterday in our telephone conversation concerning my request for temporary assignment of a physician-scientist from the Department of Health and Human Services (DHHS) to the Subcommittee staff, I am writing to provide you with examples of such temporary assignments executed in the recent past by the DHHS. Enclosed is a listing of several examples.

I fully understand your concern for not wishing to set a precedent in such matters, as expertise in science and medicine is a premium in the Federal system. However, I am sure you can appreciate the necessity for such expertise in the Subcommittee's investigation of the National Cancer Institute's Investigational New Drug (IND) Program.

As you know, the Subcommittee several months ago initiated an inquiry into the policies, practices and procedures of the National Cancer Institute. Recent findings have prompted me to direct the Subcommittee staff to focus on the NCI's IND program.

In May of this year, the Subcommittee staff obtained copies of an exchange of correspondence between Dr. J. Richard Crout, Director of the Bureau of Drugs within the Food and Drug Administration (FDA), and Dr. Vincent T. DeVita, Jr., Director of the NCI. In a letter dated April 6, 1981, Dr. Crout brought to Dr. DeVita's attention a problem regarding the NCI's failure to report in a timely fashion to the FDA adverse drug reactions of cancer patients who had participated in NCI-sponsored clinical trials. Dr. Crout raised other concerns with the NCI's IND program, including delays in submission to the FDA of annual progress reports on clinical trials, the adequacy of patient informed consent, and control over the distribution of investigational drugs. Subsequent correspondence between Drs. DeVita and Crout would appear to have resolved these issues. I am enclosing for your reference photocopies of the correspondence between Drs. Crout and DeVita.

Despite this latest understanding reached between the NCI and the FDA, recent events and discoveries pertaining to the NCI's IND program have given me cause for great concern over the integrity and efficiency of the program, which impacts on more than 35,000 cancer patients annually. The following are examples of incidents involving NCI-sponsored clinical trials and investigators:

1. On February 18, 1981, the NCI reported to the FDA that an adult patient had suffered renal failure following treatment with chlorozotocin, an investigational drug similar in chemical structure to methyl-CCNU, which also has been shown to cause renal failure.

2. The NCI reported to the FDA on March 25, 1981, that the use of methyl-CCNU may have caused acute leukemia in three patients.

3. A report from the NCI to the FDA, dated June 17, 1981, stated that four patients--three adults and one child--had developed congestive heart failure after receiving the drug dihydroxy-anthracenedione (DHAD). At least one of the three adults died of heart failure, and all three had been treated on a "protocol" not approved by the NCI.

4. On June 16, 1981, the NCI reported to the FDA the use of a radio labeled drug in four patients without an NCI-approved IND. The drug, which the NCI supplied to a pharmacologist, was to have been used for animal studies and not for clinical trial.

5. The NCI reported to the FDA on June 19, 1981, that a clinical trial, utilizing the drug deoxycoformycin (DCF), had been conducted without NCI approval.

6. Four adult patients died of liver failure after receiving the drug Indicine N-Oxide (INO), and at least two children died of liver failure possibly caused by the administration of INO.

My concerns are further buttressed by the contents of an internal NCI memorandum, which, in part, states that there is a "lack of compliance with FDA regulations in the misuse of NCI investigational agents." The memorandum contains several examples and states, "There are many others like this." The memorandum further states: ". . . I believe that I cannot ask our NCI staff to do the jobs of both meeting FDA regulations and of insuring the safe and coordinated development of our new agents while allowing this misuse of investigational agents to continue."

As Chairman of the Investigations and General Oversight Subcommittee, I am resolved to conducting a thorough and constructive inquiry into the NCI's IND program. But, again, I wish to emphasize that such an inquiry requires expertise in complex matters of biomedical research and the regulation thereof.

In light of the Subcommittee staff lacking in such expertise, it would be most helpful if you could arrange to have a suitably qualified employee of the FDA assigned on temporary duty, and at the expense of the FDA, to the Subcommittee staff for a period not to exceed 90 days. Specifically, I am requesting such temporary assignment of Dr. Michael Hensley of the Division of Scientific Investigations at the FDA. My reasons for requesting Dr. Hensley are: he is familiar with the NCI's IND program; he personally does not object to such a temporary assignment; and he and his work product are known to Subcommittee staff.

Further, I am requesting that the temporary assignment of Dr. Hensley to the Subcommittee staff be executed at your early convenience in response to the continuing potential threat to the health and safety of patients.

Should you wish to have further discussion on this matter, please do not hesitate to call me. Mr. James F. Michie of the Subcommittee staff may be reached by your staff at 244-8789.

Thank you for your cooperation.

Sincerely,

Paula Hawkins
Paula Hawkins
United States Senator

PH:jm
Enclosures

The following is a listing of individuals who were temporarily assigned from their positions with the DHHS to perform tasks for the U.S. Congress, and who remained on the DHHS payroll during such temporary assignment:

1. Dr. Robert Graham, a DHHS physician, was assigned to the staff of the Subcommittee on Health and Scientific Research for a period of more than one year during the 96th Congress.

2. Dr. George Hardy, a DHHS physician, was assigned to the staff of the House Subcommittee on Health and the Environment during the 96th Congress.

3. Dr. David Banta, a DHHS physician, served for a three-month period on the staff of the Office of Technology Assessment of the Congress in 1978.

4. Dr. Fred Bergmann, a DHHS scientist, was assigned to the Office of Technology Assessment of the Congress for a six-month period in 1979.

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

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The Honorable Paula Hawkins
United States Senate
Washington, D.C. 20510

Dear Senator Hawkins:

After receiving your letter of July 9 concerning your request to have Dr. Michael Hensley detailed to the staff of the Investigations and General Oversight Subcommittee, I explored our policy on details further.

Regrettably, I conclude that the detail of this Food and Drug employee to assist in your proposed Subcommittee review of the National Cancer Institute (NCI) Investigational New Drug (IND) Program would create an unnecessary conflict. I do not believe that it is appropriate to detail an employee from one Agency of the Public Health Service to the Legislative Branch to investigate another Agency of the Public Health Service.

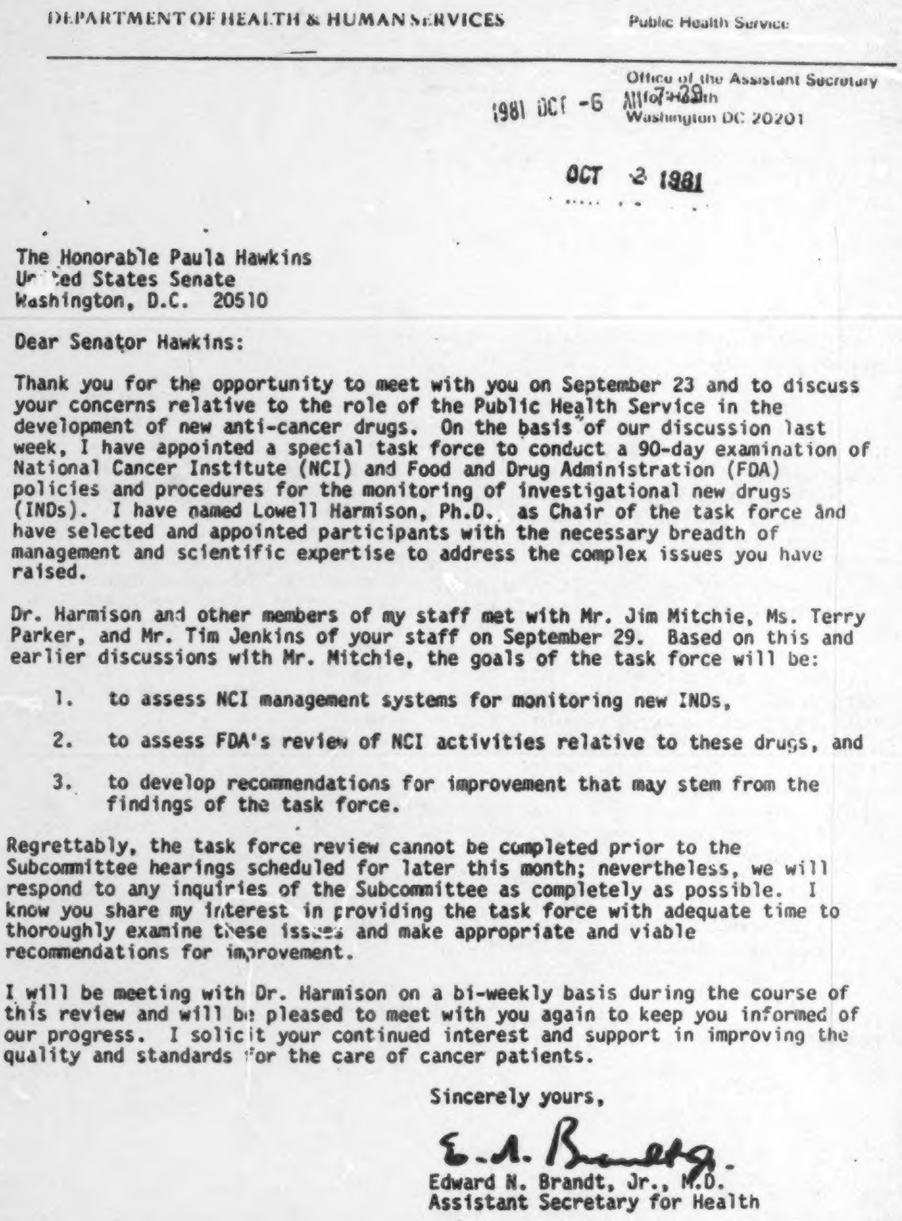
However, I am very concerned, as you are, about proper management and use of investigational agents by the NCI and the potential threat to the health and safety of patients in the event of misuse. Since the issue at hand is primarily a question of how we are managing this Department program, I have an alternative suggestion which should provide both of us with a full, objective assessment of the NCI/IND subject. To further address my own concerns, I have asked the Assistant Secretary for Health, Dr. Edward N. Brandt, to conduct a full, third-party review of this matter and to report his findings to me within 90 days. We would be glad to reflect the Subcommittee's views and questions in that review, to brief you as the review progresses, and to provide the report to you as soon as it is prepared. We will at that time discuss any further action you think may be needed. In addition, I have directed the Assistant Secretary for Legislation to continue to make available to you appropriate Departmental staff for consultation on a timely basis.

I trust this approach will be of use to you, and I have asked Dr. Brandt to contact you so we may begin our review as soon as possible.

Sincerely,

Dick Schweiker

Richard S. Schweiker
Secretary



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

1981 OCT -6 AM 7:29

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The Honorable Paula Hawkins
United States Senate
Washington, D.C. 20510

Dear Senator Hawkins:

Thank you for the opportunity to meet with you on September 23 and to discuss your concerns relative to the role of the Public Health Service in the development of new anti-cancer drugs. On the basis of our discussion last week, I have appointed a special task force to conduct a 90-day examination of National Cancer Institute (NCI) and Food and Drug Administration (FDA) policies and procedures for the monitoring of investigational new drugs (INDs). I have named Lowell Harmison, Ph.D. as Chair of the task force and have selected and appointed participants with the necessary breadth of management and scientific expertise to address the complex issues you have raised.

Dr. Harmison and other members of my staff met with Mr. Jim Mitchie, Ms. Terry Parker, and Mr. Tim Jenkins of your staff on September 29. Based on this and earlier discussions with Mr. Mitchie, the goals of the task force will be:

1. to assess NCI management systems for monitoring new INDs,
2. to assess FDA's review of NCI activities relative to these drugs, and
3. to develop recommendations for improvement that may stem from the findings of the task force.

Regrettably, the task force review cannot be completed prior to the Subcommittee hearings scheduled for later this month; nevertheless, we will respond to any inquiries of the Subcommittee as completely as possible. I know you share my interest in providing the task force with adequate time to thoroughly examine these issues and make appropriate and viable recommendations for improvement.

I will be meeting with Dr. Harmison on a bi-weekly basis during the course of this review and will be pleased to meet with you again to keep you informed of our progress. I solicit your continued interest and support in improving the quality and standards for the care of cancer patients.

Sincerely yours,

E. N. Brandt

Edward N. Brandt, Jr., M.D.
Assistant Secretary for Health

Dr. BRANDT. The task force has been now organized, has been meeting, has begun interviewing those persons who are responsible for various stages of the drug development program. It has been collecting data from those people who are both involved and many of whom have been critical of the system as well as those who assist in the development.

The role of the task force, as I said, it is very broad. They are, in fact, working very hard. We have detailed a number of people who are working virtually full time on it. I think they are making significant progress in their data-gathering activities.

Senator HAWKINS. On pages 10 and 11 of your prepared statement, Dr. Brandt, you state that the monitoring and drug distribution efforts of the NCI, the regulatory monitoring functions of the FDA, and the important role played by IRBs at research institutions around the country provide a framework for scientific research that allows for innovation while protecting the patients.

I think we all appreciate the need for innovation in these experiments with human beings, but there have recently been innovations that violate not only the rights of these patients but also the Federal regulations set up for their protection. At M.D. Anderson a drug meant for animal studies was administered to humans. And at another cancer center a combination of drugs was given to humans not only without NCI approval but also in spite of the fact that a protocol had been submitted to NCI and disapproved.

Surely, Dr. Brandt, you do not advocate this kind of innovation.

Dr. BRANDT. Well, in the first place, I do not consider that innovation in scientific research. I think the issue that I am concerned with is that, when you regulate, you are in—when you write regulations, you are in fact imposing your will upon others. I think it is unlikely that we can write regulations—I am sorry. I think it is likely that we can write regulations so tightly that we do not allow the genius and the creative thought that is present in our scientific research community to exercise itself.

I do not condone violations of regulations and codes that are set up to protect human subjects and do not advocate that in any way we develop processes and procedures that would in fact permit that or condone it.

Senator HAWKINS. On page 11 of your full statement you describe a memorandum of understanding between NCI and FDA as evidence of "the commitment of both parties to maintaining lines of communication with each other in order to exchange information and to resolve differences." We received testimony last Tuesday that revealed that this agreement is not working according to plan. Several months ago, we received a copy of this document entitled "Evolution of the National Cancer Institute Master Plan for Drug Development and Interaction with the Food and Drug Administration," generated by NCI personnel. The document accuses the FDA of having significantly delayed the use of INDs by requesting clarification of issues considered "trivial." Do you have a copy of that document? Did we give you a copy of the document?

Dr. BRANDT. No. I do not have a copy of that document.

Senator HAWKINS. The document accused the FDA of having significantly delayed the use of IND's by requesting clarification of issues considered "trivial." In addition, it states that "at the insistance of FDA and in collaboration with senior FDA staff, NCI assembled its Drug Master File, which NCI hoped would eliminate the specific problems generated continually by more junior FDA staff. Unfortunately, present actions suggest that the desirable result has not been accomplished."

The document later states that "the NCI staff are certainly willing to exert whatever effort is needed to arrive at workable solutions to these problems, but it is exceedingly frustrating when the same problems keep arising after apparently having been settled and agreed upon by senior FDA officials."

Senator HAWKINS. Do you have that document?

Dr. **Brandt**. I have the document. Evolution of National Cancer Institute Master Plan.

[The information referred to follows:]

Anticancer Drug Development; Memorandum of Understanding With the National Institutes of Health

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has executed a memorandum of understanding with the National Institutes of Health (NIH). The purpose of the memorandum is to set forth cooperative working arrangments regarding anticancer drugs developed by NIH and regulated by FDA.

DATES: The agreement became effective February 5, 1979.

FOR FURTHER INFORMATION CONTACT: Gary Dykstra, Compliance Coordination and Policy Staff (HFC-13), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3470.

SUPPLEMENTARY INFORMATION: Pursuant to the notice published in the **Federal Register** of October 3, 1974 (39 FR 35697) stating that future memorandums of understanding and agreement between FDA and others would be published in the **Federal Register**, the agency is issuing the following memorandum of understanding:

Memorandum of Understanding Relative To Anticancer Drug Development

The Division of Cancer Treatment, National Cancer Institute, as a result of its mission, has a substantial and continuing effort of anticancer drug development, the regulation of which comes under the purview of the Food and Drug Administration, primarily but not exclusively within the Bureau of Drugs. A substantial amount of the information available to the Division of Cancer Treatment and to the Bureau of Drugs, acquired by each in the pursuit of their missions, is of common interest to these organizations. In the past, both have been keenly aware of this community of interest and have had extensive informal and effective interchanges of views and of information on a wide variety of problems. Such informal interchanges should and will continue and both organizations encourage the members of their staff to provide the utmost assistance and cooperation in all appropriate areas. In addition, in order to aid in the maintenance of a harmonious, direct working relationship between these two sister organizations, both charged with responsibilities relating to public health, it is believed that a formal Memorandum of Understanding is desirable. The following specific agreements between the National Cancer Institute and the Food and Drug Administration are made to achieve these objectives:

Commitment of the National Cancer Institute

1. The National Cancer Institute designates the Director, Division of Cancer Treatment as the primary contact on matters of policy relative to anticancer drug development. Members of his/her staff responsible for specific aspects of the Drug Development Program will carry on day-to-day contact with their counterparts at the Food and Drug Administration as appropriate.

2. As sponsor of investigational drugs for clinical trial, the Division of Cancer Treatment agrees to comply with all applicable laws, regulations, and any other legal requirements pertaining to such sponsorship.

3. The Division of Cancer Treatment will transmit to the Bureau of Drugs pertinent information generated by the activities of the Division of Cancer Treatment. This will include *Cancer Treatment Reports* and copies of the minutes of pertinent meetings, e.g., the New Drug Liaison Meetings and the Phase I Working Group Meetings. These minutes are not to be considered a substitute for the annual progress reports required for each IND.

4. The Division of Cancer Treatment will designate a member of its staff as a liaison to FDA's Oncology Advisory Committee and will send members of its staff to other Food and Drug Administration meetings, as appropriate, in order to aid communication between the two organizations.

5. The Division of Cancer Treatment will maintain with the Bureau of Drugs a Master File, which will include a detailed description of its overall plan of anticancer drug development, its system of clinical monitoring, its system of drug distribution and data reporting, pertinent information on Division of Cancer Treatment staff, and other background information normally included in individual Notices of Claimed Investigational Exemption for a New Drug (also know as Investigational New Drug Applications).

When any portion of the Master File is proposed to be revised in a significant manner, the Division of Cancer Treatment will, prior to such revision, provide a draft copy of the proposed alteration for the Bureau of Drugs' comment. Less substantive revisions will be provided to the Bureau of Drugs in finalized form and such revisions will be sent with reasonable promptness. The Division of Cancer Treatment agrees to maintain the Master File in a manner which keeps it current, to add information as it believes necessary, or as requested by the Bureau of Drugs, to delete items which are no longer pertinent or active, and to submit to the Bureau of Drugs on or about January 1 of each year a list of the documents it considers to be in the Master File and a certification of their currency and accuracy.

Commitment of the Food and Drug Administration

1. The Food and Drug Administration designates the Associate Director for New Drug Evaluation, Bureau of Drugs, as its primary contact for matters of policy regarding anticancer drugs. Members of his/her staff will interact with appropriate Division of Cancer Treatment staff for day-to-day matters.

2. The Bureau of Drugs will designate appropriate members of its staff as liaison to the Decision Network, the Phase I Working Group, and the New Drug Liaison Meetings and other pertinent meetings of the Division of Cancer Treatment, to aid communication between the Bureau of Drugs and Division of Cancer Treatment.

3. In recognition of the position occupied by the Division of Cancer Treatment in antitumor drug development, and in view of the serious nature of the disease, the Bureau of Drugs agrees to cooperate with and assist the Division of Cancer Treatment in the furtherance of its objectives, to the degree permitted by regulation and law.

4. The Bureau of Drugs agrees to accept the Master File submission of the Division of Cancer Treatment as applicable to all anticancer investigational drugs sponsored by the Division of Cancer Treatment. Information in the Master File will thus be incorporated by reference into all Notices of Claimed Investigational Exemptions (IND's) for anticancer drugs sponsored by the Division of Cancer Treatment.

5. The Bureau of Drugs agrees to bring any deficiencies or problems with the Master File to the attention of the Division of Cancer Treatment as part of its review and approval of that Master File rather than as comments on specific IND's. If, after a reasonable period needed for correction of the Master File such correction is not forthcoming, the Bureau of Drugs shall inform the Division of Cancer Treatment which of

its IND's may be adversely affected and subject to administrative action.

Commitment of Both the National Cancer Institute and the Food and Drug Administration

If the Director, Division of Cancer Treatment, National Cancer Institute and the Associate Director for New Drug Evaluation, Bureau of Drugs, cannot agree on the appropriate contents of the Master File, or the approvability of the Master File or of any application sponsored by the National Cancer Institute, or on any other matters related to the regulation by the Food and Drug Administration of drugs sponsored by the National Cancer Institute, the matter shall be brought to the attention of the Director of the National Cancer Institute and the Director of the Bureau of Drugs. These persons are then responsible for jointly resolving the matter, either directly or by consultation with, or referral to, the Director of the National Institutes of Health and the Commissioner of Food and Drugs. Absent such resolution, final resolution of the matter rests with the Commissioner of Food and Drugs.

Dated: January 19, 1979.

For the Food and Drug Administration.

Donald Kennedy,

Commissioner, Food and Drug Administration.

Dated: February 5, 1979.

For the National Institutes of Health.

Donald S. Fredrickson,

Director, National Institutes of Health.

Effective date. This Memorandum of Understanding became effective February 5, 1979.

Dated: April 25, 1979.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FDA-225-79-3001]

[FR 79-13[illegible] Filed 4-30-79 8:45 am]

BILLING CODE 4110-03-M

EVOLUTION OF THE NATIONAL CANCER INSTITUTE MASTER PLAN FOR DRUG DEVELOPMENT AND INTERACTIONS WITH THE FOOD AND DRUG ADMINISTRATION

The purpose of this document is to trace historically the evolution of the Division of Cancer Treatment (DCT), NCI, Master Plan for drug development, in relation to the overall objectives of the program, and to describe some of the problems that have arisen, primarily in dealings with the Food and Drug Administration (FDA), in the course of this evolution. The interactions with FDA have centered on 3 major aspects of the drug development program: (1) the manner in which NCI submits its Investigational New Drug Applications (IND's), (2) the way NCI carries out and monitors its clinical trials, (3) the toxicology studies NCI carries out to assure the safety of drugs prior to clinical trials.

A. EARLY HISTORY

From the very beginning of the NCI drug development program in 1955, it was recognized that a national program of this magnitude and complexity required a substantial degree of uniformity to insure adequate quality control and necessary reproducibility. Thus precise protocols were developed and published for the screening of potential new antitumor agents in experimental tumor systems and in cell culture (Cancer Chemother. Rep. 1: 42-64, 1959; 25: 1-66, 1962; part 3, Vol. 2, No. 2, 1-103, Sept. 1972). Likewise, standard protocols for preclinical toxicology were also developed and published (Cancer Chemother. Rep. Part 3, Vol. 4, No. 1, 1-30, January 1973; J.N.C.I. Monograph #45, 49-56, 1977). These were adopted, in fact, as the standard by which the FDA judged the preclinical safety testing of other organizations for anticancer agents.

The early development of clinical trials presented unique problems. Because of limited numbers of patients available with a given neoplastic disease in any one institution, it was necessary to develop groups of cooperating institutions following identical protocols. As one component of the Clinical Panel that advised the NCI in the late 1950's and early 1960's, an Experimental Design Committee served to review clinical protocols and advise these groups of institutions in devising studies that would be statistically valid, scientifically worthwhile, and operationally feasible. These Cooperative Groups, as they were called, received their funds through research grants and as such, were rigorously peer-reviewed for scientific merit by a special study section of outside experts. These groups of extramural scientists are a unique resource available to NCI for drug testing. Through the combined effect of the study section review and continually increasing experience, the groups have evolved into a highly organized apparatus able to perform sophisticated clinical studies under tight quality control exerted by their statistical and operations offices. One issue continually under discussion between FDA and NCI has been the comparison of quality control of physicians hired by industry to perform drug studies vs. NCI's clinical trials groups. We believe the controls built into the NCI system are far greater, scientifically, than those of the typical physician performing studies for a fee for a pharmaceutical company.

In 1965 the NCI developed and later published (Cancer Chemother. Rep. - Oct. 1966) a detailed description of its program logic, covering all aspects of the drug development program from initial synthesis or acquisition through detailed clinical evaluation. Although specific details have been modified since that time, the overall logic remains the same. This document and those mentioned earlier provided the general outline of the drug development process through which each new drug must pass. They served as the basis for what was later to be assembled as the overall Master Plan. Clearly, from the beginning of the program, standard procedures were utilized for the individual drugs being developed, and these procedures were available and known to the scientific community, and to the FDA.

B. INTERACTIONS WITH FDA 1963 - 1975

In 1963, Congress passed the Harris-Kefauver amendments that first required the FDA to oversee the investigational testing of new drugs in humans. Between 1963 and 1975, however, the interactions between the Bureau of Drugs, FDA and the NCI were marked by a mutual attitude of laissez-faire. For instance, during a period of time before 1975 the FDA encouraged the NCI not to submit full annual reports of the status of each Investigational New Drug Application (IND). This state of affairs was a mutual agreement between the FDA Medical Officers monitoring the NCI oncological drug program and staff of the Investigational Drug Branch (IDB), DCT.

During this same period the distribution of clinical drugs to investigators throughout the United States and abroad expanded greatly as new agents were developed, encouraging results of trials were becoming known, and many new investigators became interested in studying new agents. The DCT recognized the need for better monitoring of the distribution of investigational agents, an a system evolved which required investigators who had been registered with, and approved by, the NCI to submit protocols for investigational drug use to DCT. These protocols were reviewed by DCT staff, and if approved, drug was shipped to the investigator. This system was not optimal, however, for it lacked a standard mechanism to obtain reports of efficacy and toxicity of drugs from investigators, and it did not provide adequate control over drugs being sent to independent investigators. With the arrival of a new Division Director at DCT in 1974, these procedures were reviewed and deemed inappropriate. As a result, the development of new procedures was initiated by DCT staff in 1974 and 1975 for monitoring drug distribution to cancer chemotherapy investigators throughout the United States and plans were made to limit the supply of drugs going to independent investigators (i.e. private physicians) and to improve quality control standards within clinical trials groups for the use of investigational agents.

C. DEVELOPMENT OF PROBLEMS WITH FDA - 1975

In July - August of 1975 a new team leader for Oncologic Drugs at FDA, Dr. R.S.K. Young, began raising questions about the plan for development of each individual drug for which an IND was being filed. In essence, Dr. Young maintained that the published, standardized protocols, procedures and approaches mentioned earlier were not sufficient, and each individual INDs should contain this detailed information as a separate plan for each drug. In addition, questions were raised about delinquent annual reports which, in turn, involved questions of monitoring and drug distribution, each of which will be discussed in detail later. Furthermore, FDA stated its desire to review and approve each clinical protocol after initial IND approval, in spite of the recognized expertise of NCI in this area.

Without providing NCI the time to readjust to this re-interpretation of FDA-NCI relations, the FDA began in August 1975 either to withhold the approval of new IND's submitted by NCI or to significantly delay their activation by requesting clarification of issues considered trivial or, as stated, a matter of public record. Between August and October of 1975 the FDA held up four IND submissions by NCI: maytansine, aminothiadiazole, hycanthone, and neocarzinostatin. In addition, applications from Memorial Sloan-Kettering for tetrahydrouridine, from Sidney Farber Cancer Center for aminopterin and from M.D. Anderson for peptichemio were delayed. This represented a serious and significant change from prior policies and was entirely unexpected.

Dr. R.S.K. Young admitted that the decision to enforce details previously accepted as a normal way of doing business between FDA and NCI was made following a new wave of criticism of the agency. It is interesting to note that, when Dr. Young was asked at a public meeting of the Board of Scientific Counselors of the Division of Cancer Treatment, NCI in October 1975 whether the problem of IND submissions was one of form rather than substance, he answered that it was the former.

The following example, concerning the drug maytansine, provides evidence of the kind of difficulty this abrupt change caused NCI during this period. Specifically, the FDA ignored the fact that each IND filed by NCI is based on information produced by the same development system, using the same experimental design, but felt the overall plan of drug development should be described in each individual IND application.

In responding to the INDs submission for maytansine, the reviewing officer indicated that NCI had not "provided enough detail to permit a scientific review. We looked for therapeutic rationale, but the only data we got consisted of four tables of different animal studies. We would like to know how the experiments were done and how many animals were used". In other words, the FDA was asking for specific details about how the experiments demonstrating antitumor activity were conducted. This appeared redundant from NCI's point of view, since specific protocols for the screening of new anticancer compounds were a matter of published record, as mentioned earlier, and had formed the basis of each IND submitted by NCI over the years.

Because of these types of problems, the DCT Director, Dr. DeVita, requested a meeting with senior officials at FDA to discuss the issues and attempt to resolve them. This was followed by a meeting on March 11, 1976, involving the Director, NIH, the FDA Commissioner, and senior officials of both agencies. At this meeting four major issues were identified: IND submissions, monitoring of clinical trials, record keeping and reporting, and drug distribution. As a result of these two meetings, it was agreed that FDA and NCI staff would meet frequently to discuss and resolve these major issues as well as others that may arise in the future. Furthermore, it was agreed that an overall agreement or Memorandum of Understanding should eventually be developed to delineate clearly the responsibilities and relationships of the agencies. A discussion of each of the four major issues, as well as other issues that have arisen since 1975, follows.

D. PRINCIPAL ISSUES

1. Review and Approval of NCI IND Submissions; the Development of of the NCI's Master Plan and Memorandum of Understanding between FDA and NCI

FDA justified discontinuation and disapproval of IND's in October 1975 on the basis of "inadequate information" included in the applications. In NCI's view, this often rested on extremely trivial points and/or requests for minor additional bits of information and resolution of these seemingly minor differences could have occurred more expeditiously if an informal communication (i.e. phone call) had been made and the issue settled immediately.

Of more concern to the NCI was the FDA position that development plans for each phase of development of each drug be included in every IND. In meetings with FDA, NCI pointed out that FDA was fully aware of the NCI program of drug development but FDA kept insisting it was not documented to their satisfaction.

At first, it appeared that FDA was concerned with the manner in which NCI carried out preclinical quality control. The NCI responded with the submission to the FDA in January 1976, of a document entitled "Summary of Quality Control in the Drug Development Program" (See Attachment 6 of the Drug Master File - Attachment 1). This document described the details of the quality assurance program for toxicology, formulation, production of new synthetics, animal production, and animal tumor efficacy experiments. In the course of further discussions with FDA it became clear that their concerns touched every aspect of NCI drug development including the protocol for screening, quality assurance in the preclinical development program, the toxicology protocol, the composition of internal DCT review committees, chartered peer review committees, curriculum vitae of decision makers in the Division of Cancer Treatment, and the description of the clinical trials mechanism of the NCI. It was agreed that NCI would incorporate this information into one document which would provide an overall presentation of its approaches to drug development and submit it as a Drug Master File. This document, which was developed during the course of 1976 and submitted to the FDA on December 13, 1976, outlined the DCT drug development program. This Master File contained the following documents.

1. The Treatment Linear Array which describes in detail the decision making process for the development of new drugs.
2. Organizational chart of DCT
3. Protocols for screening agents for antitumor efficacy
4. Protocols for preclinical toxicologic evaluation of cancer chemotherapeutic agents
5. Quality Control Procedures in the Drug Development Program.

A recently updated version of the Drug Master File is included for reference (Attachment 1). The initial material submitted to FDA did not outline the clinical trials activities, including the peer review system that clearly differs, as stated earlier, from procedures used by industry.

Further details of NCI clinical procedures were provided in January 1977, when the NCI submitted to FDA a document entitled "Quality Control Procedures of the Cancer Therapy Evaluation Program", which became an additional attachment to the Drug Master File. This document described the clinical trials program of the NCI including the procedures for monitoring Phase I and II studies, protocol approval, and the peer review system of the NCI for clinical trials investigators. Furthermore, it outlined a procedure for the evaluation of potential adverse drug reactions.

A more detailed plan of clinical development was provided with submission in January, 1978 of a document entitled, "Operational Plan and Procedures for Clinical Trials", which was appended to the Drug Master File, and replaced the January, 1977 document. This document described investigator selection, peer review, Cancer Therapy Evaluation Program (CTEP) organization, and drug distribution policies. One section of this document contained a detailed description of the Cooperative Group structure and function, including the monitoring carried out by the groups, methods for assuring compliance with FDA regulations, and both external and internal peer review procedures. It represented the revision of a document prepared in 1976 by NCI and Cooperative Group Staff, which had been submitted to FDA at that time.

The original "Master File", submitted in December of 1976, was approved by the FDA in principle in 1977, through their release of the long-pending IND's. After numerous meetings and revisions, some of which resulted in the addenda mentioned above, the FDA officially accepted the Drug Master File on December 27, 1979. Under its terms, the NCI is responsible to:

1. Cross-reference each IND submission to the Master File and thus provide much more streamlined information in its individual IND applications.

2. Approve new protocols for clinical trials under an approved IND and proceed with clinical trials without pre-review or approval by FDA of each individual protocol. These protocols are filed as IND amendments only. Results are communicated to the FDA in annual reports.

As an umbrella document to define the overall relations between NCI-FDA, Dr. DeVita drafted a "Memorandum of Understanding" relative to anticancer drug development in early 1977. This was submitted to the FDA on March 15, 1978. After numerous meetings and discussions, this "Memorandum of Understanding" was finally accepted by a letter dated January 19, 1979, from Dr. Donald Kennedy, the Commissioner of FDA, to Dr. Frederickson, Director of NIH, (Attachment 2). This document defines the mutual goals of both agencies in facilitating development of new drugs for cancer while adhering to regulatory requirements.

Specifically, the NCI agreed to:

1) designate the DCT Director as the primary contact person on matters of policy,

2) comply with applicable regulations and legal requirements pertaining to sponsorship of drugs under its IND,

3) provide the Bureau of Drugs with pertinent information including Cancer Treatment Reports, Minutes of the Phase I and New Drug Liaison Meetings,

4) designate a member of the DCT staff as a liaison to the FDA's Oncology Advisory Committee, and

5) maintain a Drug Master File with the Bureau of Drugs which will include a detailed description of its overall plan of anticancer drug development, system of clinical monitoring, system of drug distribution, data reporting, etc.

The FDA agreed to:

1) designate the Associate Director for New Drug Evaluation as its primary contact person,

2) designate an appropriate member of its staff to key NCI meetings including Decision Network, Phase I Working Group, and New Drug Liaison Meetings,

3) cooperate with DCT in supporting its objectives in the development of new anticancer agents to the degree permitted by regulation and law,

4) agreed to accept the Master File submission as applicable to all anticancer IND's sponsored by DCT, and

5) bring deficiencies identified by FDA on individual IND's to DCT's attention as a problem with the Master File rather than effect an abrupt discontinuation of individual IND's as the initial step.

This latter was intended to alleviate many of the specific problems that had delayed individual IND's over the previous two years.

With the adoption of this document and the final acceptance of the Drug Master File, the filing of IND's by NCI has been simplified.

2. Drug Distribution; Development of Drug Catagories A, B, & C

As mentioned in the earlier section on Early Interactions with FDA, the NCI's distribution of drugs had grown by the early 1970's to a massive effort involving large numbers of independent investigators as well as Cooperative Groups.

The FDA criticized the NCI for the fact that drugs had been distributed prior to 1975 to individual investigators often without the benefit of registered protocols and with little or no feedback regarding results of such investigations. The new Director of DCT, Dr. DeVita, agreed with this criticism.

The NCI responded that previous staff developed the system of drug distribution in recognition of the fact that few of the anticancer drugs in clinical use were available through commercial sources, and therefore the National Cancer Institute was the principal supplier of cancer drugs both for research and for treatment. Nevertheless, the NCI initiated a major revision of its system for drug distribution, since it would otherwise be impossible to effect adequate monitoring and reporting of NCI-sponsored clinical trials (see Issues 3 and 4, below).

In January of 1977, the DCT worked out a functional system for distribution by classifying drugs into three categories. This system was formally presented to the FDA's Oncologic Drugs Advisory Committee in April of 1977 and was accepted in principle. Fundamentally, drugs were divided into three groups:

1) Group A were Phase I and single agent Phase II drugs which should be distributed only to highly qualified clinical investigators experienced in the use of new agents.

2) Group B were drugs which were being tested in broad scale efficacy studies, but still restricted to investigators who had demonstrated their qualifications through peer review. Furthermore, another valuable resource in the cancer program was utilized, namely the cancer centers. Centers were to distribute certain Group B drugs to investigators whom they deemed to be qualified to perform Phase II studies.

3) The Group C category was established at this time to bridge the so called "drug gap". It was felt that it was necessary to have a means to distribute drugs for which a clear and consistent pattern of efficacy had been demonstrated. Such unmarketed drugs must alter the pattern of care in a particular tumor type, even if beneficial effects on survival may not be demonstrated. Drugs in the Group C category, therefore, were to be made available to physicians who were registered with the NCI (FDA Form 1573) and were to use the drug for the stated indication in compliance with the "guidelines protocol". The monitoring responsibilities of the NCI for these drugs were understood to be minimal and limited specifically to reporting of adverse drug reactions.

Furthermore, this mechanism of Group C would permit as rapidly as possible the availability of major new advances in cancer chemotherapy to the patient community during the frequently long interval between the demonstration of efficacy and the approval of an NDA submitted from a pharmaceutical company.

The establishment of this mechanism eliminated broad-scale distribution of all classes of agents to so-called independent investigators (usually private physicians) and provided them only with those agents which had a demonstrated role in patient care.

On August 2, 1976, the FDA officially notified NCI of approval of Group C status for the following agents: daunomycin, 5-azacytidine, streptozotocin, CCNU, MeCCNU, BCNU. Since that time, an additional six drugs have been approved under Group C. Of these twelve drugs, six have received NDA approval and are now commercially available. A list of these drugs is appended (Attachment 3).

In summary, the NCI now maintains a complete record of every shipment of cancer drugs and has done so for approximately the last decade. Drugs are made available only to qualified investigators who meet criteria which are set forth in great detail in the Operational Plans and Procedures for Clinical Trials document, which is a part of the Drug Master File. The system of classification of drugs into A, B, and C was further defined by the requirement that the designation of the drug in a Group C category for a specific indication would require the approval of the FDA's Oncologic Drugs Advisory Committee and FDA staff.

3. Monitoring Clinical Trials

Pharmaceutical houses generally contract with private firms to design and monitor clinical trials for their new drugs. These firms provide data for the drug house which in turn provides them to the FDA. The contract firm frequently selects physicians in an *ad hoc* fashion and compensates them to perform these studies. These physicians perform their work outside of any peer review system other than the monitor. These private firms monitor the quality of data on the data sheets and check the results. FDA had indicated during the meetings in 1976 that NCI should emulate this approach. NCI's response was that the monitoring of clinical trials in grant and contract-supported work by the National Cancer Institute was superior to that required of industry because peer review assured the highest quality investigators. This system, however, uses entirely different safeguards. The principal safeguard in the peer review system, is that investigators are not compensated financially, but rather by the reward of the judgment of their peers on the scientific merit of their efforts. This system, which includes not only publication in scientific journals and presentations at national and international scientific meetings but also requires reporting of data at regular meetings at NCI, was felt by the NCI to provide a superior system of checks and balances. Furthermore, both the individual grantees and the clinical cooperative groups are subject to the scrutiny of periodic formal site visits and peer review committee evaluation which is far more rigorous than any which exists in the pharmaceutical industry. Not included, however, is on-site monitoring of patient flow sheets and records.

For NCI contractors, monitoring is conducted not only by the peer review system but also by the NCI project officer and at regular meetings of the working group for Phase I-II drugs. In the cooperative groups, monitoring is aided by the presence of NCI staff at the cooperative group meetings as well as internal review of data by the study group chairman and the group statistical office, and presentations at least twice a year at cooperative group meetings.

Several discussions between NCI and FDA have centered on the necessary degree of monitoring in relation to data that may be crucial to approval of a New Drug Application (NDA). It is clear that some NCI-sponsored studies (e.g. Phase I, Phase II single drug studies) fit that category, while the majority of sophisticated and complex Phase III and Phase IV combined modality studies carried out by the Cooperative Groups are ancillary to NDA considerations, since they are largely disease-oriented rather than drug-oriented. In view of that fact, the NCI has determined that for the necessary close monitoring of the Phase I-II program, a formal system of contract-supported monitoring should be established. Therefore in October of 1979, the NCI contracted with a commercial firm to provide on-site monitoring of individual patient data records for all patients entered into the Phase I-II studies supported by the NCI. Note that this monitoring does not replace or alter the peer review process to which the Phase I-II investigators are subject. This system was described in detail to the FDA at the NCI-FDA meeting in August 1980. FDA agreed that Cooperative group studies would not require the same degree of monitoring as Phase I-II studies, realizing that results of group studies may not be accepted by FDA as directly contributory to an NDA. It was agreed that NCI would attempt to identify specific studies in the Cooperative Groups that might provide data essential to an NDA, and in such cases closer monitoring would be provided.

As mentioned above (Issue 2) it had become impossible to monitor adequately clinical studies by the large number of independent investigators previously receiving drugs from NCI. With the elimination of that distribution, monitoring of all NCI-sponsored studies, as outlined here, became feasible and effective.

4. Record Keeping - Annual Reports

One of the FDA concerns was NCI's lack of timeliness in providing annual summary information on active INDs, which is a statutory requirement. The NCI admitted its deficiencies in this area, at least part of which resulted from the widespread distribution of drugs and concomitant difficulty in obtaining data (see Issue 2). In 1976 additional staff were recruited to perform these responsibilities and also, as described above, NCI eliminated the supply of drugs to independent investigators. This reduced the reporting task to one of feasible magnitude. Furthermore, many relatively inactive IND's were closed (about 40). At this time the NCI holds approximately 100 IND's and produces approximately eight to ten annual reports per month. Although we have had reporting problems in the recent past, at present we are in total compliance with the requirements for annual reports and we intend to maintain that compliance.

E. OTHER ISSUES

In addition to the above major issues in the years of 1975 through 1979, there are a number of other issues which are or have been under discussion. These will be listed briefly:

1) Therapeutic Intent -

A staff member of the Division of Oncologics of the Food and Drug Administration raised an objection to informed consent forms. He felt the comments on the forms relating to therapeutic intent during Phase I trials were coercive. During a long series of discussions, senior NCI staff clarified that Phase I studies in cancer patients are unique because these studies are conducted upon the very population for whom the treatment is ultimately intended. The median survival of these patients is about 6 months and more than 90% are dead in one year. Therefore, no patient is ever treated in any Phase I study without the prospect of a therapeutic benefit. As simple as this may seem, it occupied a great deal of time during meetings between the NCI and the FDA.

2) IND's for Combinations of Cancer Drugs -

FDA staff strongly suggested on a number of occasions that use of cancer drugs in combination would require a separate INDs and should therefore be preceded by combination animal toxicology testing.

From a scientific point of view it made little sense to perform these evaluations in animals since the intent is to manipulate the therapeutic index -- that is, the ratio between the therapeutic benefit and the side effects or toxicities caused by the drug. It should be noted that animal tumors do not predict precisely for therapeutic effect in human tumors, but serve effectively to reduce the universe of potential agents for clinical evaluation and to establish relative priorities. Therefore, basing the selection of potentially useful combinations on animal data would be of limited benefit and require enormous expense. The NCI proposed and finally the FDA agreed to the current system of extremely careful initiation of combination studies. Such work is conducted by expert investigators, well experienced in the use of chemotherapeutic agents.

3) Drug "Promotion"

FDA has viewed press coverage concerning presentations by NCI intramural/extramural scientists at national scientific meetings as "promotion" of drugs before efficacy and safety have been demonstrated. Since "promotion" is prohibited by regulation, they have protested to NCI. However, it should be noted that these regulations clearly apply to pharmaceutical houses with a commercial interest. As an example, a senior scientist in the Developmental Therapeutics Program of the NCI made a presentation about his own laboratory research at an international scientific meeting involving a drug on which NCI held an IND. This presentation provoked a letter from the FDA and a formal complaint to the NCI that the presentation at that scientific meeting represented promotion of the drug. Such a charge appeared to NCI to be frivolous.

4) Analytical Quality Control

FDA staff have frequently raised numerous questions concerning chemical aspects of IND submissions, many of which are considered trivial. Fortunately, by agreement with senior FDA officials, these questions have not delayed approval of new submissions but they have required extensive efforts to research and respond. On occasion, more serious problems have arisen and one example is described below. In May 1980, the NCI initiated a clinical trial of intravenous and oral amygdalin following a lengthy review of its IND Application by the FDA. On September 5, 1980, NCI received an urgent phone call requesting a meeting between senior staff of FDA and NCI.

This meeting was called because an assay report by the Chief of the Instrumental Application Branch at the FDA, stated that the amygdalin product of the NCI had a purity that was close to 70% rather than the 90% which was indicated in the NCI IND. At substantial expense of both time and money, additional tests were run on short notice at the NCI contract analytical laboratory at Stanford Research Institute (SRI) and the project director was brought to Washington to present his data at the meeting. Minutes of that meeting indicated that senior staff of FDA conceded that the FDA's interpretation of their own data was in error. Moreover, the FDA chemist reran the assay as suggested by NCI and in an internal memo dated October 7, 1980, stated that the results were now in agreement with NCI data. This entire incident resulted in consumption of a significant amount of senior staff time as well as contractor effort and almost halted an ongoing trial that had taken three years to initiate, an overall effort in which the senior FDA staff had actively participated.

F. TOXICOLOGY PROTOCOL -- A CURRENT MAJOR PROBLEM

As mentioned in the section on Early History, the NCI had developed and utilized for many years a standard protocol for preclinical toxicology testing of new anticancer agents. This protocol had been accepted as the national standard.

By 1977, however, NCI recognized that certain changes in this standard protocol were both scientifically and economically worth considering.

The protocol required that toxicology studies be done in both dogs and monkeys. Monkeys are very expensive, difficult to obtain, and more important contribute very little additional useful toxicology information not revealed by the dog studies. Furthermore, the magnitude and complexity of the protocol precluded its use by smaller organizations desiring to undertake their own drug development programs.

Based on analyses of the toxicities of anticancer drugs in other animal species and man strongly suggesting that a change in the approach would be both safe and effective (Attachment 4), NCI proposed development and consideration of a simplified protocol. The new protocol eliminated the monkey and used primarily the mouse. This protocol was widely discussed and commented upon publicly, including a review by the Board of Scientific Counselors of the Division of Cancer Treatment. After numerous discussions with FDA staff, and preliminary consideration by the FDA's Oncologic Drugs Advisory Committee, the NCI presented its proposal to a special subcommittee of the FDA Committee on July 9, 1979, and to the full Committee on October 11-12, 1979. The Committee recommended approval of the new protocol on a trial basis, with certain modifications, to which the NCI agreed.

One specific change involved the histologic examination of animal tissues. NCI maintains that histopathology has provided little useful information to the Phase I-II investigators, and therefore had not planned to review histology slides until the drug had demonstrated efficacy. In addition, NCI proposed, as one option, using the mouse alone as its primary test species. The Advisory Committee hesitated to take those steps they suggested another option in which dogs would be studied at 1/10 the LD_{10} dose in mice. In addition, they suggested the histology slides be read during the Phase I trial period in order not to delay initial clinical trials. NCI agreed to these changes.

On February 6, 1980, the FDA gave verbal approval to the new protocol, as revised, and an official addendum to the Drug Master File was submitted March 7, 1980. Since that time [illegible] has begun to implement the new protocol, and five agents developed under this new protocol should be ready for IND filing in the next four months. Within the last few weeks, NCI received a telephone call from FDA requesting a meeting because of questions raised by FDA staff about the protocol. In a memo of March 31, 1981, to the Associate Commissioner for Health Affairs, FDA, Dr. Crout has stated that he has instructed his staff not to approve INDs based on data obtained from the new protocol, the major issue apparently being the timing of the histopathology. In spite of the agreement of the FDA's Oncologic Drugs Advisory Committee, and permission from senior FDA officials to proceed under the terms mentioned above, other FDA staff have continued to object and apparently brought about this action. If maintained, this decision would halt the progression of many potentially life-saving compounds through the NCI drug development network. A meeting with FDA was held on April 27, 1981, at which NCI presented it position, but FDA has not informed NCI of a decision thus far.

G. CONCLUSION

In summary, the NCI has had for many years, well-developed, organized, and generalized approaches to the preclinical and clinical development of anticancer agents. At the insistence of FDA and in collaboration with FDA senior staff, NCI assembled its Drug Master File, which NCI hoped would eliminate the specific problems generated continually by more junior FDA staff. Unfortunately, present actions suggest that this desirable result has not been accomplished. The net effect is a continuing requirement for senior staff time and effort at both FDA and NCI to meet and resolve numerous issues. This is neither efficient utilization of manpower, nor efficient in terms of the rapid and effective development of new and better cancer therapies. NCI staff are certainly willing to exert whatever effort is needed to arrive at workable solutions to these problems, but it is exceedingly frustrating when the same problems keep arising after apparently having been settled and agreed upon by senior FDA officials. It is hoped that this problem can be resolved.

SUMMARY OF GROUP C DRUGS

Drugs Approved Since Group C Program Inception

	Date of Group C Approval	Date of NDA Approval
BCNU	8/76	5/77
MeCCNU	8/76	
CCNU	8/76	10/76
5-Azacytidine	8/76	
Streptozotocin	8/76	
Daunomycin	8/76	5/80
L-Asparaginase	10/76	4/78
Erwinia L-Asparaginase	2/78	
Cis platinum	7/77	12/78
Hexamethylmelamine	7/77	
VP-16	5/78	
THC	10/80	

Senator **Hawkins**. Yes. Would you look at the last page?

Dr. **Brandt**. All right.

Senator **Hawkins**. Do you feel that this kind of document fosters and encourages a good relationship between your two agencies?

Dr. **Brandt**. Well, I have not read the whole thing; but, reading just this last page, I would say certainly that this is not the kind of document that I would like to see in terms of the two agencies working together and developing the kind of relationship that is essential to address this critical problem. I will, in fact, read the document. Can you, Madam Chairman, tell me the source of this?

Senator **Hawkins**. The NCI

Dr. **Brandt**. From the NCI?

Senator **Hawkins**. It came from the NCI.

Do you think it appropriate to refer to a junior FDA staff?

Dr. **Brandt**. Think it appropriate to?

Senator **Hawkins**. Yes.

Dr. **Brandt**. It depends on—it is quite common in the scientific community to refer to younger scientists as junior.

Senator **Hawkins**. Are there agreements made between senior staff that junior staff do not know about?

Dr. **Brandt**. There should not be agreements made with senior staff that junior staff were not aware of, no. I am sure that on occasion that does happen, but it surely should be communicated from senior staff to all of the people who are concerned.

Senator **Hawkins**. So, it is your opinion that there should not be, but, if there has been in the past, it should be corrected?

Dr. **Brandt**. It is my opinion that there should not be for those persons who are directly concerned. I do not think that it is necessary for the FDA senior staff that works with the NCI staff to necessarily communicate agreements to all people in the FDA who are not involved directly in the approval process for anticancer drugs.

Senator **Hawkins**. Dr. Brandt, on page 12 of your full statement you say that the Master Drug File lists the clinical investigators who conduct early human trials of cancer drugs, their qualifications, and the facilities in which they work.

Last Tuesday, Dr. Hoth of the NCI acknowledged that the Institute still does not know the identities of all of its investigators. Were you aware of that?

Dr. **Brandt**. I was not aware of Dr. Hoth's statement until he made it that they are not aware. Perhaps Dr. DeVita might like to add something to that.

Senator **Hawkins**. We will refer this to Dr. DeVita when his time comes.

Dr. Hayes has a time problem. Are we encroaching upon your time? Dr. Hayes, what time do you have to——.

Dr. **Hayes**. I am due to be outside at 10:30, Madam Chairman.

Senator **Hawkins**. Let us turn to Dr. Hayes. We will return to Dr. Brandt since Senator Kennedy is not here right now anyway.

Dr. Hayes, we heard rather disturbing testimony from FDA employees that were subpenaed to appear before the subcommittee on Tuesday, and I recounted some of the testimony in my opening statement. Would you address the concerns raised by the physicians and scientists from the Food and Drug Administration?

Dr. **Hayes**. Which specific concerns, Madam Chairman, that there was favoritism or that they are being pushed?

Senator **Hawkins**. The frustrations and concerns of FDA personnel. Have you had occasion to talk to any of them?

Dr. **Hayes**. No, not since the testimony.

I am constantly faced with individuals in the Food and Drug Administration that have frustrations and concerns and for a variety of reasons, not all of them scientific, and most of them having nothing to do with NCI, as I am sure you are aware.

I am very concerned when the people in the agency which I lead have concerns or frustrations. On the other hand, I think there is a world of difference between suggestions, allegations, and complaints and what in fact is true or demonstrable. I think there is no question that individuals see things quite differently. Some may feel that in 1 minute they are being pushed and the next minute things are too relaxed. And, as I am sure you are aware, the Food and Drug Administration and not infrequently the Commission are accused of going in two exactly opposite directions at the exact same time, too little and too much, too fast and too slow.

There is no question that efficiency and promptness in the review of scientific materials, whether from NCI or a drug firm or an academic institution, is very much a part of what the FDA should be doing. And I have told people in the Food and Drug Administration all the way down the line that I think efficiency and promptness is important, that there is no value in desultory action or in delay.

That does not mean, and I have never implied, and I am quite surprised if anybody has inferred, that that statement on my part or any of the senior managers including the bureau directors at this time or in the past, for that matter, means that they are supposed to practice bad science. I have been a scientist too long to countenance that, and I think I would have to see some very strong proof before one would be able to fairly accuse me or the agency management that promptitude and efficiency in getting on with the job to approve scientific documents so that drugs can be developed, tested and evaluated and, if appropriate, used in patients as marketed drugs means that it is supposed to be based upon indefensible or bad science.

Senator **Hawkins**. We are not here to accuse anyone of anything. The witnesses were here under oath and stated their concerns as scientists. You are new, we understand, at the agency.

Dr. **Hayes**. I am new to the agency, but I am not new to science, Madam Chairman.

And don't misunderstand. I do not feel accused. All I am saying is that I think it should be said for the record with respect to what has been said in testimony at this and other hearings on this subject and related subjects, that the push, as it has been described, for promptness and for efficiency in reviewing documents as well as all the other things for which the agency is responsible does not imply and nothing, to my knowledge, has been said or intimated from which it could be inferred that this means that the values, the criteria or the science underlying these decisions is to be compromised. And I do not believe that there is a natural antagonism or antipathy between those two.

Senator **Hawkins**. Prior to the hearings Tuesday were you aware of the apparent discord between your agency and the NCI?

Dr. **Hayes**. Yes, Madam Chairman. I know that there has been discord and there has been concern and anxiety, if you will. On more than one occasion I have discussed this with Dr. DeVita as well as with Dr. Crout, the Director of the Bureau of Drugs within the agency. Indeed, before he resigned as Director of the National Institutes of Health, I spent an afternoon discussing this with Dr. Frederickson in the context of the relationships between the Food and Drug Administration and the National Institutes of Health, both in terms of regulation, science, exchange of information, personnel, and the like.

I think that I have fairly addressed this in my discussions with Dr. Crout and the actions that have emanated from that as well as with Dr. DeVita and most especially and most recently in the participation by Food and Drug Administration officials on Dr. Brandt's task force.

Senator **Hawkins**. I have a memo before me dated March 24, 1981 from Jerome Halperin, Deputy Director, Bureau of Drugs, to M. J. Finkel, M.D., Associate Director for New Drug Evaluation, which states that "As a sister agency in the Public Health Service, we do have a special relationship with NCI, even though some people find that difficult to understand and accept. Thus, the mere act of sending a letter to NCI, which for all practical purposes is a regulatory letter, is an unusual if not unique step for us." That is in the memorandum.

[The memorandum referred to follows:]

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Marion J. Finkel, M.D.
Associate Director for New Drug Evaluation

DATE: MAR 24 1981

to Dr. Kelsey
for action.

FROM : Deputy Director
Bureau of Drugs

SUBJECT: Letter to NCI

I have read George Blatt's memorandum to you of March 11, the draft letter to Dr. DeVita, and your note to Dr. Crout of March 14. He and I have discussed this issue and have agreed with the strategy that you have outlined, i.e., the letter should be sent but Dr. DeVita should be alerted that he will receive the letter and we should agree to hold meetings with NCI promptly to help them bring NCI monitoring and adverse reaction reporting and IND reporting obligations back into compliance quickly.

The letter itself, however, needs a good deal of editing for style and clarity. You did a brief amount of editing on it and I did a brief amount of editing, but as I read it over, it lacks a proper introduction as well as a statement of the policy and regulatory implications of the problems. While I can understand how the letter has been drafted this way, i.e., it is similar to the letters we send out to other sponsors, there is a difference between a commerical sponsor and the National Cancer Institute that has not been grasped well in this draft. As a sister agency in the Public Health Service we do have a special relationship with NCI, even though some people find that difficult to understand and accept. Thus, the mere act of sending a letter to NCI, which for all practical purposes is a regulatory letter, is an unusual if not unique step for us. The letter should carry some of that flavor. We should point out that we have tried before to bring problems to NCI's attention, through the periodic meetings between NCI and the Bureau. We have attempted to impress upon NCI the need to adhere to its obligations as a sponsor and a monitor. I would not pull any punches in terms of the facts in the letter. The charges are well substantiated and they should, indeed, be made known to DeVita. The issue is how they are couched and what the policy implications are for this letter.

In the event that the letter may become a public document through an FOI request it must meet the test of both substance and style. If you will revise the letter and send it forward again, Dr. Crout has agreed to sign it.

Jerome A. Halperin
Jerome A. Halperin

Senator HAWKINS. Were you aware of this memo, and does it reflect your policy as Commissioner of the Food and Drug Administration?

Dr. HAYES. I was not. Dr. Crout was. He can speak to that if you would like, Madam Chairman.

I am not exactly sure I know how to respond to your question, does this reflect our policy. I think I can say this about the relationship between the Food and Drug Administration and any body or any institution with whom we deal, be it within the Government, such as the NIH and NCI, or regulated industry or universities, independent institutions. And that is that the law and the regulations are for everyone. I hope and I believe that, in general, our enforcement of those regulations is fair and equitable and the same for everyone. That is not to say that, for certain institutions—and not necessarily those in Government exclusively at all—that in terms of management or the way we in fact enforce those regulations may differ. How I enforce the regulations is not only my responsibility, but it is that for which I am accountable. It is up to me to do it in the way that I think is the most efficient.

That does not imply that there is a lesser standard for the National Cancer Institute. Indeed, I think the record shows, even though there have been individual exceptions or problems or at least allegations thereof in this particular case, that the Food and Drug Administration is often toughest on agencies within the Government, not excluding itself. As I am sure you are aware, we give ourselves a very hard time in our GLP inspections and the like. I think, if we were looking for a place for favoritism, we might well start at home.

So, I think the record is rather clear that does not preclude the fact that there have been and, I am sure, in the future in our relationships with any organizations including those within Government that there will be problems, whether at a personal level or just a fluke in terms of a lost piece of paper or something did not get reported.

We try to do it better. We try that all the time. But I do not see that anything is special with respect to our relationship to NCI. And, to return to the bottomline answer to your question, in terms of regulation and accountability, they are treated no differently than anyone else inside or outside of the Government. How we do it, I think, is my responsibility as long as the end result is the same and not unfair or inequitable.

Senator HAWKINS. Are you aware of the fact that it took 7 months for the Bureau of Drugs to issue the notice of adverse findings to NCI pertaining to NCI's failure to report serious and fatal reactions to Methyl-CCNU and two other drugs of the nitrosourea class?

Dr. HAYES. That it was 7 months? I am aware. Yes, ma'am.

Senator HAWKINS. In light of the seriousness of this particular matter, do you feel it was necessary for the Bureau of Drugs to take so long in issuing that notice to the NCI, especially since the investigation and findings of the FDA's own inspections had been completed in 1980?

Dr. HAYES. Well, I think there may be some considerations in this particular case which I cannot address since they all antedated me, and I cannot speak to them firsthand. I think, if you would like, Dr. Crout can.

I think that there is no question that, without reference to facts here with which I was not involved, that one should act as promptly as possible. Nowhere is that more important than with respect to adverse drug reactions and their reporting. I think it is also important that we not, however, do it so promptly that we are not sure that we are talking about something that is an adverse reaction and that we frighten people. I think that this is one of the judgments that has got to be made. I think promptitude is clearly important for adverse reactions that are so identified.

Senator **Hawkins**. Are you going to look into that? I know that predated you.

Dr. **Hayes**. I am very much in the middle of looking into all this, Madam Chairman.

Senator **Hawkins**. Going back to the staff problems, is there any mechanism within the FDA to insure that you are regularly informed of staff-level problems?

Dr. **Hayes**. Do you mean within the Bureau of Drugs or elsewhere? Well, I think so. I am working very hard and have since I became commissioner a few months ago to organize not only the chain of command and responsibility and delegation of authority but also the information coming up as well as going down. In an agency of 7,500 people scattered in 50 States and 19 buildings within this metropolitan area, that is not always easy.

I have been looking for—and, I think, in some areas already successful—in establishing a means of communication. One of these is meetings with the bureau directors on just these sorts of subjects.

I also might point out that I meet with the individuals within the bureaus at every level including the, quote, "junior scientists," unquote. And I would like to do that all the more. There are certain time constraints. I am not sure the system ever will be perfect. But I think I have a reasonable idea of what is going on.

Senator **Hawkins**. Dr. Hayes, one closing question. Senator Kennedy is supposed to return. Dr. Brandt stated in response to my request for a task force update that interviews have been conducted with officials in responsible positions. Have you been interviewed?

Dr. **Hayes**. Not yet. I think maybe they are saving me toward the end.

I know that a number within the agency have been interviewed. As I mentioned, there are some individuals not from the Bureau of Drugs who, in fact, are members of that task force. But I have not yet been interviewed formally by the task force.

Senator **Hawkins**. Do you feel that the regulation of anticancer drugs is too strict?

Dr. **Hayes**. Is too strict?

Senator **Hawkins**. Yes.

Dr. **Hayes**. No, I do not think I can say that overall. I think that perhaps in the past there have been some areas where we have not appreciated the special nature of cancer drugs, the patients for whom they are designed, the very special nature of certain parts of the testing, for example, phase I, routinely, of course, done for a therapeutic and in patients rather than, as with most drugs, in normal volunteers.

So, I think there are some special concerns from a medical and pharmacologic and chemical consideration. And I think, perhaps, in some areas we in fact have picked on small points that were not appropriate to those drugs. But in general I think the treatment has been fair. It is strict, but then it is still a very important aspect of clinical testing.

Senator HAWKINS. Have you ever seen the flow chart of adverse drug reaction that we have upon the easel? [1]

Dr. HAYES. No. I do not think I have. It is a little hard to read it from this distance, Madam Chairman.

Senator HAWKINS. Do you have a copy of that? We had it in small form Tuesday.

Dr. HAYES. If this is the flow chart from the master file, then, in fact, I have seen it, not written so large.

Senator HAWKINS. Yes, that is what that is. I was wondering what your opinion of the chart is?

Dr. HAYES. Well, I am not sure that I have any scientific opinion except that those that have reviewed this seem to feel that it is a reasonable way to proceed. I am not sure that it is a perfect way or that there will not be changes. In terms of whether scientifically this is a reasonable approach, my area is not cancer drugs. If those were cardiovascular drugs, I could give you a better scientific opinion. I do rely upon the review of this, both within the agency, the NCI, and outside that it is a reasonable but, I am sure, not perfect way of proceeding at this time.

Senator HAWKINS. You do not perceive it as administratively difficult?

Dr. HAYES. Well, you know, even the simplest procedures when you write them out in flow diagrams can be seen to be or one can infer that they are administrative nightmares. I think it is important in an area as complicated as this and with all of the potential problems in studying these very powerful and poisonous drugs in a very serious and usually fatal condition that we attempt by monitoring and reviewing and revising if necessary the system so that there are not administrative problems or delays or we are not tripping over paper, so to speak.

On the other hand, as we have discussed earlier this morning, I am always a little concerned that we not take streamlining as the absolute goal and then find out that, in fact, we were not doing something scientifically or, from the standpoint of patients, ethically that we should be doing. It is a balance, Madam Chairman, as it is in the study of any drugs. And I think that eternal vigilance, as elsewhere, is the cost.

Senator HAWKINS. We appreciate your coming today. Since Senator Kennedy has not returned, we will excuse you in time for your appointment.

Dr. HAYES. Thank you very much, Madam Chairman.

Senator HAWKINS. Thank you. I look forward to your improving the morale and the administration of the FDA.

We will return to Dr. Brandt.

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[1] Flow Chart of Adverse Drug Reaction (ADR) may be found on p. 212.

You mention in your statement that you are addressing the problem of drug accountability. You say there is a new system which is going to be "piloted" this year. Will this pilot study start soon? When can we reasonably expect a program to become operational?

Dr. **Brandt**. It will become—the pilot program will become operational in January 1982.

Senator **Hawkins**. Eighty-two?

Dr. **Brandt**. Yes, ma'am. Approximately 6 weeks from now or so.

Senator **Hawkins**. You also speak of the President's Commission for the study of Ethical Problems in Medicine and Biomedical and Behavioral Research in your statement. How would you characterize the liaison between the Commission and the Department of Health and Human Services?

Dr. **Brandt**. The liaison between the Commission and the Department at the present time is—well, let me just speak for myself; I cannot speak for the whole department. I have not met with the people from the President's Commission at all up until now.

Senator **Hawkins**. We are very interested in the task force. You mention in your statement that the mission is broad. You refer in general terms to the review of management structures and policies of the NCI and FDA. Could you be more specific regarding the task force charter? Is there anything in writing?

Dr. **Brandt**. Yes. Yes. There is the purpose of the task force and the appointment. The purpose of the task force lists three principal objectives. One is to assess the National Cancer Institute management system for monitoring new investigational drugs; second, to assess the Food and Drug Administration's review of NCI activities relative to these drugs; and, three, to develop recommendations for improvement that may stem from the findings of the task force.

I have left it broad because I do not want to try to prejudge the issue either from newspaper accounts or other or my own view but, instead, to attempt to allow these experts to go in, look at these systems, be as open and objective about it as possible and to make the appropriate recommendations to me for implementation.

Senator **Hawkins**. What are the qualifications of the members, for example?

Dr. **Brandt**. They cover a broad range of persons who have a wide variety of backgrounds. I can give you a few examples if you would like. The chairman of that task force is Dr. Lowell Harmison, who is my science adviser. He has long experience in dealing with management of scientific affairs and is one of the more competent managers.

Dr. Lionel Bernstein serves as the vice chairman. Dr. Bernstein is a distinguished physician who has much experience in the evaluation of drugs, not in cancer but in other areas, who has served in a variety of capacities including currently as director of the Lister Hill Center at the National Library of Medicine.

It includes also persons who have experience in the evaluation of drugs in other areas. It includes management people, professional management people. It includes an epidemiologist. It includes two lawyers. It includes a person whose concerns are system organizations.

Senator **Hawkins**. Do you know if any members have any experience in oncology?

Dr. **Brandt**. None of them have any direct experience in oncology.

Senator **Hawkins**. What about toxicology?

Dr. **Brandt**. In toxicology; yes.

Senator **Hawkins**. Who is that member?

Dr. **Brandt**. Dr. Harmison is familiar with toxicology and with the operation of the national toxicology program.

In addition to that, of course, we have made the full complement of the Public Health Service available to them. Should they, for example, have concerns about toxicology, they are perfectly open to, perfectly free to call for any experts in toxicology to gain information from them.

Senator **Hawkins**. Have any of the members worked in the chemotherapy field?

Dr. **Brandt**. No, not to my knowledge. I should say not to my knowledge.

Senator **Hawkins**. Will the task force make recommendations at the completion of its review?

Dr. **Brandt**. Yes, they will.

Senator **Hawkins**. When can they be expected and who will make the final decisions regarding their implementation?

Dr. **Brandt**. I will.

You asked when. Their current timetable is that they are to present me with a report at the end of this year.

Senator **Hawkins**. The end of this year?

Dr. **Brandt**. Yes, ma'am.

Senator **Hawkins**. December?

Dr. **Brandt**. I am sorry?

Senator **Hawkins**. Do you have a specific date in December?

Dr. **Brandt**. I think, actually, that it is January the 4th or 5th. I cannot tell you the exact day. I have forgotten.

Senator **Hawkins**. When is their next meeting? Do you know?

Dr. **Brandt**. They meet virtually daily. I do not know when their next meeting is. I am sure they are not meeting today, but they meet virtually every day, either as a body or as individuals.

Several of these people on the task force have been assigned full time. That is all they do, is work on this task force.

Senator **Hawkins**. Do you consider it a deficiency not to have an oncologist on the task force?

Dr. **Brandt**. Do I consider it a deficiency?

Senator **Hawkins**. Yes.

Dr. **Brandt**. Well, I think that one can look at that, I guess, in a whole variety of ways. I think they have access to a lot of oncologists who can serve this as an internal task force. To find an oncologist meant that I had to go within the NCI to do so, since we are looking at the NCI, that did not seem appropriate to me.

Senator **Hawkins**. It did not seem appropriate to you?

Dr. **Brandt**. It did not seem appropriate to have someone from the National Cancer Institute serving on this task force. Since that is the source of oncology experts, it did not seem appropriate to do it. They are, however——

Senator **Hawkins**. You could not get an oncologist——

Dr. **Brandt**. I am sorry?

Senator **Hawkins**. You cannot get an oncologist that is not with the NCI?

Dr. **Brandt**. Well, that is where our expertise is in the Public Health Service, in oncology.

Senator **Hawkins**. Thank you, Dr. Brandt, for coming. Senator Kennedy might have some questions of you. We are going to go to Dr. DeVita at this time.

We appreciate your cooperation extended to the Subcommittee, Dr. DeVita. I thank you for taking the time to appear before us today.

As you know, a group of your employees and a former employee of the National Cancer Institute testified on Tuesday before this subcommittee. These witnesses, I think it is fair to say, acknowledged the fact that there have been and still are problems with the National Cancer Institute's drug development program. As we asked Dr. Brandt and Dr. Hayes earlier, in light of Tuesday's testimony, please describe the existing problems as you see them.

Dr. **DeVita**. Yes, Madam Chairman. I heard of their testimony. And I certainly agree that one of the most difficult areas I think we have to face is the issue of adverse reaction reporting, which will take continual attention on our part.

One of the difficulties with adverse reaction reporting which is illustrated, I think, by some of the cases that you have mentioned—nitrosoureas, DHAD, and other drugs—is that they usually go in three phases. There is a phase when we all look at the data. That includes NCI and FDA staff at our joint meetings. And we see data but we do not recognize an adverse reaction.

There is a stage when we suspect an adverse reaction. And then there is a stage when we finally all agree we have one. And then at that point with the benefit of hindsight one can go back to the first phase and realize that we were seeing it at a time when we did not recognize it as an adverse reaction.

I think the failure to appreciate those three phases has caused a little bit of confusion. Our error that we discussed with you at our last committee meeting, in May, with the drug methyl-CCNU, was in working up the adverse reaction at the suspected phase without notifying the Food and Drug Administration until we were satisfied that we clearly had an adverse reaction. That system has now been changed so that we notify the Food and Drug Administration promptly of suspected adverse reactions.

I should point out, however, as a consequence of doing that, we have reported at least one and probably two adverse reactions that are not adverse reactions, which is the risk in this system, that we will put in too much information. One of these relates to methyl-CCNU, and I would like to describe it for you, because it actually led to an observation that is scientifically of some importance. We reported shortly after the last committee meeting that methyl-CCNU also seemed to be associated with leukemia in some of our studies. So we did a very careful analysis and found out that when you look at patients who were treated with methyl-CCNU and compared them to a population such as you and I and Dr. Crout and Dr. Brandt and all the people in this room who do not have colorectal cancer, where the drug is used for treatment, there is a significantly higher incidence of leukemia. We immediately reported that reaction and disseminated the information to our investigators.

However, when you compare the incidence of leukemia in people who have colorectal cancer who have not received methyl-CCNU, you find that there is also a higher incidence of leukemia and there is no significant difference. So, we may not be seeing an adverse reaction due to this drug. What we may be seeing is that people who are predisposed to one cancer are also predisposed to a second cancer.

My personal feeling about the problem is that it is better to err on the side of reporting a potential reaction. I just illustrated an example of how complicated the adverse reaction area can be. When one looks at those three phases, you are seeing the data, but you are not seeing the reaction. You suspect a reaction in the second phase. You prove it, and then with hindsight you go back to the first phase. This, by the way, was the source of the confusion and the inaccuracies in the Washington Post series. With the benefit of hindsight, those reporters were able to go back to the phase when everyone looked at the data and no one could see the sequelae of it.

So, I think adverse reaction reporting will always be a problem. We are in the process of educating our staff. We are in the process of educating our investigators by sending out notifications and by announcing at regular meetings that we want to be notified of each and every adverse reaction so that we can promptly report it to the Food and Drug Administration.

Madam Chairman, I think Dr. Hoth presented evidence at the hearing on Tuesday that in fact demonstrates that we have reported a number of adverse reactions at an accelerated rate in the past year as a result of added attention to this particular factor.

Senator HAWKINS. I am sure that everyone here appreciates the movement not only at your Agency but also at Food and Drug Administration to improve and tighten up the policies, practices and procedures of these agencies. However, it is apparent from this subcommittee's 7-month-long investigation that all is not well. While the reporting of adverse effects appears to have improved in recent months, why did it take so long for the NCI to mail to the clinical investigators a letter calling attention to the importance of immediate reporting of adverse reactions among patients treated with investigational drugs supplied by NCI, a letter dated October 26, 1981,[1] which is just a week ago?

Dr. DEVITA. That is just part of a process, Madam Chairman. I do not believe it is the only process. In other words, for example, we have five phase I and II meetings a year. And the first steps that were taken, for example, when Dr. MacDonald was notified of Dr. Bono's concern that was mentioned earlier, were to immediately notify the investigators at these meetings of the seriousness of reporting adverse reactions.

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[1] Memo dated October 26, 1981 to Clinical Investigators, from Bruce A. Chabner, M.D., may be found on p. 214.

So, we use several ways of doing it. And that was just one of a series of steps that we have taken to continually remind our investigators.

Senator HAWKINS. Was this sent to all the investigators?

Dr. DEVITA. It is my understanding it has been sent to all our clinical investigators, yes.

Senator HAWKINS. And you know who they all are?

Dr. DEVITA. Well, yes, we do, in large part. The reference to the satellite investigators is an interesting one. As you know, we are expanding our program to involve community oncologists. The first step—actually, it took place a couple of years ago—was to allow the clinical cooperative groups to develop satellite relationships with community hospitals so that the community physicians could take part in research efforts. These are ongoing programs that will become part of the community hospital oncology program that we are setting up in response to your last hearing.

We do not at the moment know the identity of each of the practicing oncologists who are joined with the cooperative groups. These data are being sent to us and will be in our files. But in terms of our——.

Senator HAWKINS. As of this moment, you do not know the identity of all of your investigators?

Dr. DEVITA. At this moment there are some satellite investigators we do not know. But all grantees and contractors, yes, we know their identity.

Senator HAWKINS. But you are instituting a procedure whereby anybody using NCI-sponsored experimental drugs would be known to you?

Dr. DEVITA. Yes. We know where the drugs are going and to what protocols they relate. The drugs are sent out in amounts sufficient to cover the protocol. Dr. Brandt mentioned the issue of leakage. I would like to comment on that because each time we set up a system to distribute drugs to do what he pointed out, that is to control their distribution on one side, at the same time leave access to them to patients who need them, there are problems that develop with each system that in turn require correction.

Dr. Crout and I faced the problem of drug distribution back in 1974 and in 1976 set up this group A, B, C system which really restricted distribution of cancer drugs rather markedly compared to previous procedures. It seemed to be a way we could really control distribution and have a good idea of where the drugs were going and how they were being used. Prior to that time, the Food and Drug Administration had a rather heavy burden of compassionate INDs. That is, patients who felt they needed a drug would call the Food and Drug Administration and get permission from them to use a drug that NCI supplied. And we would supply the drug to those patients. Group A, B, and C restricted that considerably and took a burden off the Food and Drug Administration. But it created the problem of leakage of drugs that were unused and were not returned to the NCI, we think, for patients for compassionate purposes. In other words, instead of calling the NCI and asking us to release it under a compassionate IND or calling the Food and Drug Administration for release under compassionate IND, a physician would call some doctor who had a drug in the group B category that was on its way to group C but had not quite made it yet and would get a compassionate release of the drug. And we think to some extent that is going on. And we now have this new drug accountability system that to which you have already referred will tighten that up so the drug will not be usable. It will have to be returned by our site visiting contractor who will actually site visit the institutions that receive these drugs periodically and check their log books during the site visit.

This however, Madam Chairman, will create a problem of returning the burden of compassionate INDs to the Food and Drug Administration and the NCI which we will have to handle in a different way.

Also, when we set up, the community clinical oncology program, and you will hear from Dr. Moertel later today, we hope to be able to restrict the group C drugs, for example, to physicians who are part of this program. This will help us keep track of those drugs. It will also help us control the "leakage" situation. On the other hand, it will create additional problems because, although we can do this because we will have a lot of community programs around the country, and that means that although patients will have access to them, there will still be physicians who will no longer have access to drugs in group C. And they will have to turn either to the community programs or to the Food and Drug Administration, or to the Cancer Institute in order to get these drugs.

We hope they will turn to the community programs because that is the purpose of setting them up. But we will have to set up some sort of accountability system with those community programs so that the drugs used are those that are used under the proper control mechanisms with the National Cancer Institute.

So, every time we take what we think is a positive step, it does create additional problems in that we have to change the systems. And we intend to change them to stay in compliance with all the FDA regulations.

Senator HAWKINS. Dr. DeVita, I am sure you are familiar with a memo that was written by Dr. Vincent Bono dated April 30, 1980.[1]

Dr. DEVITA. Yes, indeed.

Senator HAWKINS. Concerning the "lack of compliance with FDA regulations and the misuse of NCI investigational drugs." In this memo Dr. Bono spoke of clinical trials of drugs that had not been approved by the NCI. Dr. Bono suggested that those responsible should be punished and that as long as these illegitimate studies continued he felt he could not, quote, "insure the safe development," unquote, of NCI's drugs.

In retrospect, do you feel something else should have been done, perhaps a letter to your clinical investigators instead of, as Dr. Bono put it, using "persuasion and education"?

Dr. DEVITA. Well, what was done was that Dr. MacDonald discussed this with Dr. Bono, and there was an upcoming meeting of our phase I working groups. So, the information was transmitted at the phase I working group.

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[1] Memo, dated April 30, 1980, from Bono to Associate Director, CTEP, may be found on p. 4.

We also, knew what these protocols were. It isn't that they weren't approved. We knew they were in existence. They were the kinds of protocol that we would have approved. We are dealing with investigators who in this case have made many important advances that are in large part responsible for those 46,000 patients a year that are curable by chemotherapy. So, these are not bad protocols, but they were protocols that were done in advance of NCI approval.

I think we have that situation under control now although I am sure we will see a protocol or two in the future that will be started without NCI approval. But we have made it quite clear to our investigators that without adequate communication it is impossible for us to disseminate not only adverse reaction information but positive effects that individuals see so that we can begin to take the next research steps. That is also part of our responsibility, to pick up on new leads very rapidly so that we can translate that into a therapeutic benefit.

I think that, if there had been protocols that raised questions of patient safety and patient risk and we knew they were going on, we should have taken other steps. But they were not. They were protocols that were good therapeutic attempts. So, no further steps were taken except to inform the investigators that we would not permit this to happen again.

Senator Hawkins. In light of what we know now, do you think a letter should have been sent?

Dr. DeVita. I do not think that what has happened since would have been affected by a letter Madam Chairman, but one does not know about this in retrospect.

I think the situation really is quite good now in terms of investigators getting preapproval of protocols.

Senator Hawkins. Last Tuesday Dr. Hoth testified that the reason animal study data, critical to formulation of protocols with adequate warning, was not forwarded to the FDA nor to the clinical investigators was because of an "internal administrative lapse". I speak of animal data pertaining to the cardiotoxicity of the drug DHAD.

Dr. DeVita. Yes, that——

Senator Hawkins. Just exactly what did Dr. Hoth mean by that?

Dr. DeVita. Yes, that is a very interesting point, Madam Chairman. I should point out that to this day, we do not know that DHAD really produces cardiotoxicity. All we may be seeing in the clinic is the expression of cardiotoxicity related to the previous treatment with the drug adriamycin. But we have in fact warned our investigators of the possibility.

The second point is that the toxicity for that particular drug was done under our previous system, which relies on the beagle dog as its main determinant of cardiac toxicity. And the cardiotoxicity data that we had and sent forward did not in fact indicate that this drug was cardiotoxic.

It is not, by the way, as some people have assumed, a drug that is related to adriamycin. It only has very limited similarities to adriamycin.

There was a study done on rabbits that was available after the clinical trials had begun which should have been forwarded as part of the information package. It should be made very clear that that study, had it been done before the clinical trial, would not have prevented the clinical trial from going ahead. We know we need better drugs in those patients who respond to adriamycin, and we do not necessarily stop the clinical testing of drugs that might have cardiotoxicity.

The other point is the rabbit model was never one of our primary models in developing judgments about putting drugs into clinical trials.

The final point is that the report was sent to one of our staff members and sat on that staff member's desk for a period of time that was unacceptable, but should have been forwarded.

The point I was trying to make is the forwarding of it would not have influenced any of the decisionmaking or probably the outcome of what has happened with DHAD including the fact that we to this day are not 100 percent sure that this drug has any cardiotoxicity at all.

Senator HAWKINS. You still feel that way in light of what FDA said Tuesday about the drug?

Dr. DEVITA. I think that at this point in time, Madam Chairman, we do not know that this drug is cardiotoxic. I was not here when the FDA was testifying. So, I am not sure what they said in reference to this particular drug.

Senator HAWKINS. Nevertheless, have you warned your investigators about——

Dr. DEVITA. That is correct. We have warned them just to be on the safe side because there have been 5 deaths out of 1,200 patients treated with this drug, which is the incidence one would expect, because the population treated has been largely exposed to adriamycin. Five out of 1,200 is about the incidence of cardiac deaths you would expect from exposure to adriamycin itself. It is hard at this point for us to distinguish between the past effect of adriamycin and the effect of DHAD, but we are, again, trying to err on the side of reporting adverse reactions that might exist even if we are not sure they are there.

Senator HAWKINS. What have you done to make sure that studies do not sit on people's desk like the one in this instance?

Dr. DEVITA. I made very clear to my staff that this kind of communication system——

Senator HAWKINS. Is that senior staff or junior staff?

Dr. DEVITA. Yes, indeed, Madam Chairman.

And this particular individual is no longer with us.

Senator HAWKINS. In testimony on Tuesday, Mr. Meade, who is an FDA inspector, testified that the files of the cancer therapy evaluation program were in complete disarray and very disorganized. Can you tell us if you have done anything to correct this?

Dr. DEVITA. I think the impression of complete disarray is not entirely accurate. We have multiple files because we are dealing not only with IND files but with files on clinical studies and files on our plans for future research efforts in clinical studies. And one has to go to multiple files to get some of the information.

It will never be possible for us to combine them all in one because if we put all the research effort files into the IND files, then I think we would have a hard time getting information out of the IND files.

I think that we have a complicated program. We have 80,000 people a year who are on one type of research effort or another. Only about 40,000 of those have a drug involved. The rest have other things like radiotherapy and other kinds of approaches to treatment. So, we have a confusing array of files. People who are not used to looking at them but——

Senator HAWKINS. You think an FDA inspector is not used to looking at files?

Dr. DEVITA. I do not think that they are used to looking at the files to the same extent at a pharmaceutical house, for example, as they would find at the NCI. The pharmaceutical houses do not have a clinical trials program the size of ours. They usually have very limited clinical facilities and a smaller number of IND's, particularly in the cancer drug area. I do not know of any pharmaceutical house—I would be glad to find one—that has a clinical trials program with 80,000 patients a year on research protocols. I do not think there are any.

Senator HAWKINS. So, you have no plans for improving the filing system?

Dr. DEVITA. Oh, we plan to improve them a good deal. We would like to have them all computerized so that we can have much more rapid access to data. We have done some of this. So, as technology improves, we will continually try to improve the files so that we can cross-index them.

We have had this problem in the preclinical area, too, Madam Chairman. We have two sets of data in the preclinical area: Biologic data on the effectiveness of drugs in animals, and chemical data. They are in two sets of files. Our staff has examined numerous ways of keeping them separate but being able to read the chemical data at the same time you are looking at the biological data. And that takes improvements in computer technology, the hardware and software, and a good deal of money. We are constantly looking at this.

Senator HAWKINS. Mr. Meade's very recent report on the inspection of the NCI beginning in July of this year, quoted two of your managers as suggesting that the FDA was on a "fishing expedition." What do you think he meant by such a comment?

Dr. DEVITA. Well, I should point out, Madam Chairman, that it is not rare for anyone, including NCI staff, not to like to be investigated or regulated. Some of the comments that you see in memos and in documents like the one that we were referring to earlier come from staff who feel that they are trying to do their job and they have to stop what they are doing to provide information for someone who appears to be looking for something very vague. So, I suspect that that is the source of a comment like that.

My staff, on the other hand, clearly understand that, when the FDA wants to come and fish, that they are entitled by the regulations to come and fish if they want. We have opened our files. I do not believe there is any institute I know in the Federal Government and probably no organization our size in the world that has opened its files in the last 2 years to more people in more ways than the Cancer Institute.

So, there may be a few of those memos around, but we will continue to allow fishing expeditions if that is what is required.

Senator HAWKINS. How many patients are effected by the use of NCI-sponsored drugs? Do you know?

Dr. DEVITA. Well, we know the total use of drugs that are commercially available that practicing doctors can use. I have guessed that some 200,000 people a year in this country are receiving chemotherapy. I think it is a reasonable estimate. Some people say it is a little too low.

In our own protocols, phase I, II, and III protocols, a total of 32,000 are treated, with smaller numbers for phase I and larger in the later phases. And there are some phase IV protocols, where drugs are compared to other kinds of treatment such as surgery.

So, the totality for drugs is about 45,000 of the 80,000 we have on research protocols. But the totality of use in this country is probably in the region of 200,000. So, there is a fair awareness of chemotherapy amongst our population in this country that was not there, say, 10 or 15 years ago.

Senator HAWKINS. How many investigators—I think we discussed this earlier——

Dr. DEVITA. I believe we have 6,000 to 6,500 investigators involved.

Yes; and I should comment on the issue of investigators. If I can go back to my statement, for example, there are different levels of investigators. The phase I investigator is not only known but carefully monitored. The phase II and III investigators are all known and are grantees and contractors. And the phase IV investigators also fall in that category.

But there are different grades of investigators depending on the kind of research in which they are involved. The newest investigator that we are trying to involve—and I think a major mission of the cancer control program—is the practicing physician. This person has not normally been considered a part of our investigative pool, but we hope in the future by setting up this clinical program he will become an investigator in the normal sense of the word, as a participant in the research effort of a clinical trial.

Senator HAWKINS. I am sure that you are aware of the requirements in the Federal regulations that state simply and mandate that all investigators be advised of any findings associated with the use of the drug that may suggest side effects.

Dr. DEVITA. Yes.

Senator HAWKINS. We are providing you with a copy of Federal regulation 312.1A6, which states:

> The sponsor shall promptly investigate and report to the Food and Drug Administration and to all investigators any findings associated with the use of the drug that may suggest significant hazards, contraindications, side-effects, and precautions pertinent to the safety of the drug.

Do you see that?

Dr. DEVITA. Yes, indeed.

Senator HAWKINS. Would you agree with me that each investigator physician administering these drugs to patients should have the complete report of all suggested side effects and precautions pertinent to the safety of these drugs?

Dr. **DeVita**. I believe that that is a reasonable act. I think the only worry I have, Madam Chairman, is the use of the word "suggested." For the reasons I mentioned earlier, if we suspect an adverse reaction, the answer is an unequivocal yes. Suggested side effects are included in our clinical brochures based on our knowledge of what these drugs do in animals, so that investigators who are testing these drugs in the early phases are in fact given all this information.

Yes, I agree under those circumstances.

Senator **Hawkins**. It seems to me that it would be impossible for the NCI to abide by the Federal regulations until you have a listing of all investigators——

Dr. **DeVita**. We do, Madam Chairman. We really do. We should not misconstrue the individuals who are in the satellite programs as being the same as investigators who are doing phase I and II testing. The individuals in satellite programs are often using the commercially available drugs in protocols that are already in the phase II category. I will give you an example. The national surgical breast group, which is testing drugs like phenylalanine mustard, a drug which has long been marketed, to compare the effect of surgery alone or surgery plus radiotherapy in breast cancer to surgery plus chemotherapy, has satellite investigators. But that drug is commercially available.

There is a big difference between investigators who are doing phase I and II testing and investigators in the terms that I mentioned, in satellites using drugs that are commercially available and operating within the realm of medical practice. Our problem there is a data collecting problem as opposed to adverse reactions.

But, in fact, if phenylalanine mustard, for example, which is an old drug, has an adverse reaction reported, it is reported to the sponsor, which in this case would be the company that markets it. And then the company that markets it does send out an announcement to all physicians. Usually they will mail very widely to all physicians in the country, in the event that they will use it and including our cancer investigators. And so will we if we get these kinds of reactions.

I think that our investigators, the ones testing new drugs in their various phases, are fully informed of adverse reactions. We know who they are. They are basically in 10 institutions that are very tightly monitored by this clinical trials monitoring system.

I did not bring with me a sample of the monitoring package but I wish I had because it is a fairly impressive document. And they are visited three times a year. We know who they are, Madam Chairman. I want to stress that.

Senator **Hawkins**. So, you are telling me that there are no investigators that do not have access to the information?

Dr. **DeVita**. There are no investigators in the phase I and II testing that have no access——

Senator **Hawkins**. How about phase III and phase IV?

Dr. **DeVita**. In phase III and phase IV, you get to the situation that I referred to, where you are dealing with commercially available drugs, which we would notify everyone if something came up. But by that time these drugs have usually been around for a very long period of time and it is unusual to see adverse reactions at that point. And then that is the responsibility again of the marketer of the drug, and they do that, I think, quite well.

Senator **Hawkins**. I am intrigued by your correspondence with Dr. Crout. You wrote a letter to Dr. Crout dated May 8, 1981. Do you have a copy of that letter?

[The information referred to follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND [illegible]

NATIONAL CANCER INSTITUTE

MAY 8 1981

Dr. J. Richard Crout
Director
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20857

Dear Dr. Crout:

I am writing in response to your letter of April 6, 1981, in which you raised a number of questions concerning the nephrotoxicity discovered with the drug, Methyl CCNU, as well as other points about NCI's sponsorship of drug trials and its reporting to the FDA. I will respond in order to each of the points in your letter.

A. Requirements for Prompt Reporting of Serious Adverse Reactions to FDA

As you noted in your letter, the NCI Drug Master Plan includes a detailed flow chart for dealing with potential adverse drug reactions. When possible adverse reactions are reported by an investigator, the NCI drug monitor is required to check the clinical information about the drug and to convene the inhouse Adverse Drug Reaction Committee which may then decide to classify the adverse drug reaction as "definite," "possible" or "not likely." In the case of the initial reports on Methyl CCNU brought to the attention of our staff, the extremely long time intervals between drug administration and renal lesions, as well as the existence of multiple other factors, raised serious questions concerning a direct relationship between the drug and the reaction. Because of these uncertainties, the NCI decided to classify the renal insufficiency as "possible but not definite drug reaction" and at the same time develop additional information before filing an Adverse Drug Report with the FDA. Nonetheless, the NCI notified members of the Brain Tumor Study Group and the major users of the drug. It was not until early in 1979 that definitive information, consisting of the written report from Dr. Harmon, led the NCI staff to conclude a clear relationship. At that point, about 1,100 investigators carrying out treatment with the drug were notified of the adverse reaction, and a formal Adverse Drug Reaction Report was filed with the FDA.

One might conclude that the time involved in carrying out this evaluation was greater than should have been the case, but I must point out that reactions occurring after such a long period of drug treatment in cancer patients are not at all easy to classify. Although animal toxicology studies with Methyl CCNU and the other nitrosoureas clearly showed evidence of acute renal toxicity, the lack of such effects in early clinical trials suggested that the animal toxicology studies represented false-positive results. We believe we have been responsible in reporting adverse drug reactions when firm conclusions have been drawn concerning such possible reactions. Incidentally, I have been unable to find any reference to a specific 15-day reporting time in our Drug Master Plan.

We have reviewed our system of reporting of adverse drug reactions, and we believe it is functioning well at this time. This can be best described by detailing the steps we have taken with a recent Adverse Drug Reaction Report. During March of 1981, the NCI became aware of a number of cases of acute leukemia in patients previously treated with Methyl CCNU. The FDA was notified by telephone during the last week of March and more formally in writing within several days. At the same time, a letter was mailed to all investigators (approximately 1,000) utilizing Methyl CCNU, cautioning them that this complication had been observed. Simultaneously, we initiated a chart review of the major clinical studies employing this drug in adjuvant settings similar to that of the original cases. When this review is completed, it should be possible to determine the incidence of leukemia among several thousand patients treated with Methyl CCNU. A panel of hematopathologists is being convened to review the slides from these cases, following which it is anticipated that the results of this investigation will be presented for publication in a medical journal as well as through the Division of Cancer Treatment Bulletin. If it is determined that a positive association has been established, we will file a formal Adverse Drug Reaction Report. In addition, other steps will be taken, including: 1) any new protocols submitted utilizing this agent will be required to include this complication in the protocol text as well as in the informed consent, 2) the guidelines protocol for Group C distribution will similarly be modified, and 3) we will establish an ongoing surveillance of the existing protocols in which patients may be at risk for this complication. We believe this represents a maximum effort on the part of DCT to pursue a potential adverse drug reaction.

Furthermore, the NCI is now taking additional steps to assure that the oncologic community remains aware of the general procedures for reporting possible adverse drug reactions. A notice is currently being prepared for mailing to all NCI investigators detailing their responsibilities to report adverse drug reactions to NCI. In addition, the NCI has reminded the Chairmen of the clinical cooperative groups of their responsibilities in this area and has asked them to communicate this to their membership.

Finally, we intend to review these procedures annually for adverse drug reactions reporting in order to identify any problems. This would be done one to two months prior to updates of the Drug Master Plan. In summary, the NCI believes that this system is functioning in a manner appropriate to the purpose of informing investigators as well as protecting patients from unneeded harm.

B. Requirement for Prompt Reporting of Serious Adverse Reactions to Clinical Investigators

1. Intramural Investigators

As noted in Part A, we did not consider the adverse drug reaction of Methyl CCNU to be established until February 1979, even though Dr. Jensen-Akula's letter of November 13, 1978, suggested that it was a possibility. In attempting to review what occurred between February 1979 and May 1979, however, we find that there probably had been some lack of communications between our Cancer Therapy Evaluation Program and our intramural Clinical Oncology Program. We cannot determine the exact cause of the problem, but we have taken steps to assure that it does not occur again. For instance, we will insure that without exception all intramural protocols are entered into the computer file in our Investigational Drug Branch, so that the intramural investigators will automatically receive any notices that are sent to extramural investigators. This apparently was the problem in the case under question.

2. Extramural Investigators

As you note, the Brain Tumor Study investigators were notified in June 1978 of a possible adverse drug reaction. Other investigators were not notified because, as stated above, the relationship had not yet been firmly established. As also noted in Part A, once the relationships had been confirmed, all investigators were notified.

C. Delay in Revision of Protocols

With regard to the revision of the intramural protocol, the comments in Part B.1. are relevant. Thus, Dr. Fisher did not incorporate a change in his protocol until official notification of the adverse drug reaction had been received by the intramural Clinical Oncology Program, which apparently did not occur until May 1979. I have no specific explanation for the protocol from the Northern California Oncology Group, but we will insure through careful monitoring that changes in protocols are made as soon as information justifies such action.

D. Requirement for Submittal of Annual Progress Reports to the IND

We have recently reviewed all of the IND's under NCI sponsorship and did, indeed, find some for which annual reports were overdue. It is my understanding that all annual reports are currently up-to-date, and we will see to it that this situation persists.

E. Informed Consent Requirements

With regard to the intramural project, the comments in Parts B and C pertain.

F. Requirements for Continuing Review of Studies by IRB and for Reporting of Adverse Reactions to IRB's

A March 23, 1981, letter from Dr. Petricciani to Dr. Lipsett pointed out that not only NCI but all of NIH was apparently operating under procedures that were not consistent with FDA regulations. The NIH has now changed its rules so that we will be in compliance with FDA regulations in this regard.

G. Control Over Distribution of Investigational Drugs

As we have discussed on many previous occasions, the NCI procedures for controlling the distribution of investigational drugs during the early 1970's left much to be desired. This is one of the reasons that NCI and FDA developed the current distribution plan. As you noted in your letter, our present procedures provide much tighter control over drug distribution, and we believe the problems that were apparent during those early years will not occur in the future.

In summary, I believe that our investigation of the nephrotoxicity of Methyl CCNU was carried out in accordance with the spirit of our Master Plan, although there may be some differences of opinion concerning the speed at which that investigation proceeded. As noted above, we have made certain changes in our overall procedures that we believe will improve our monitoring of possible adverse reactions and our general oversight of investigational drug studies.

I would be happy to discuss these matters with you at your convenience.

Sincerely yours,

Vincent T. DeVita, Jr., M.D.
Director
National Cancer Institute

Dr. DeVita. No, but I recall it.

Senator Hawkins. It states that—

> Because of these uncertainties, the NCI decided to classify the renal insufficiency as possible but not definite drug reaction and at the same time develop additional information before filing an Adverse Drug Report with the FDA. It was not until early 1979 that definitive information * * * led the NCI staff to conclude a clear relationship.

These are your words. You concluded in the May 8 letter, which we will provide you a copy of:

> We believe we have been responsible in reporting adverse drug reactions when firm conclusions have been drawn concerning such possible reactions.

Do you have that letter?

Dr. DeVita. Yes, I do.

Senator Hawkins. The Federal regulations speak in terms of clearly requiring you to report to the FDA and to all investigators any findings that suggest side effects, do they not?

Dr. DeVita. Yes, Madam Chairman.

Senator Hawkins. Yet you are talking in this letter in terms of establishing definite drug reactions, are you not?

Dr. DeVita. That is correct. That was clearly a misunderstanding on our part with the Food and Drug Administration. Remember, the first renal toxicity with nitrosoureas were reported to occur 4 years after exposure to the drug. So, again, with the benefit of hindsight we think that there really are renal toxicities. But the first physicians who saw them were not sure they were dealing with a drug-related effect.

We thought and in the way we had outlined that adverse reaction diagram you have, that we had freedom to work up a reaction within the guidelines of the master file. It seems terribly silly of us, frankly, not to go ahead and let the FDA know that we were working up an adverse reaction. Had we notified the FDA, we would have proceeded to do exactly the same thing, that is to be very careful and scholarly about working up the adverse reaction. That takes time. And we would not have had any difficulty.

In this case it was a misunderstanding of the language of the document, and Dr. Crout and I have agreed that we will notify the FDA of a suspected reaction and then work it up.

Again, I wish to emphasize the difference between a suspected reaction, a proven reaction, and that very gray area when all of us are looking at the data and not seeing an adverse reaction. So, a suspected reaction is further down the line.

In that case we were remiss in the sense that we should have notified the FDA we were working it up. But I do not believe, Madam Chairman, it would have changed things.

I want to point something out to you that I think is interesting and that is——

Senator HAWKINS. You said you would not change things?

Dr. DEVITA. I do not believe it would have changed how we worked up the methyl-CCNU because——

Senator HAWKINS. And yet you suggested you were terribly remiss——

Dr. DEVITA [continuing]. It just takes time for us to work up these adverse reactions.

For example, consider the climate of how that information came in to us. Between 1971 and 1977 we did not see any renal toxicity in clinical studies in patients treated with nitrosoureas, and therefore it was not possible prior to 1977 for us to include in an informed consent form that you might expect to have renal toxicity. The first case that was reported to us, which in retrospect seems a clear case of nitrosourea tox——

Senator HAWKINS. Have you ever followed the Federal regulations?

Dr. DEVITA. We follow them very closely, Madam Chairman.

Senator HAWKINS. This is the only lapse?

Dr. DEVITA. There are other lapses, and there will be other lapses, I am sure. But I think, as a matter of policy, this was an issue where the FDA and the NCI——

Senator HAWKINS. In some instances I have problems with the way regulations are written. You know, they are very hard to understand. They are very confusing, and you have to get a lawyer maybe to interpret both sides of how a regulation is written.

In this instance it is so simple. So, it is just mind boggling that we——

Dr. DEVITA. We all certainly agree that the policy and the procedure for us to follow is to report to the Food and Drug Administration suspected adverse reactions. And I think that in this case we should have done that, and there should not have been the confusion in the language. Somehow or other, it seems clearer, again, with the benefit of hindsight because the nitrosourea renal toxicity issue is a very complicated issue. It looks clearer now that it is all worked out, but there were some people who did not believe we were seeing renal toxicity; and therefore we did not have a suspected reaction. But there is no argument now. We agree that we should do that. I have instructed my staff——

Senator HAWKINS. It seems so simple and clear to me.

Dr. DEVITA. That is correct.

Senator HAWKINS [continuing].—That that is one regulation that is clearly understood without having to be interpreted.

Also mentioned in your correspondence with Dr. Crout was the adverse drug reaction flow chart, which is a part of your Drug Master File. That same chart is the one that is displayed on my right.

Dr. DEVITA. Yes.

Senator HAWKINS. Was not the purpose of the chart to describe the adverse drug reaction reporting system which was in effect at the time?

Dr. DEVITA. Yes.

Senator HAWKINS. Did you approve that plan?

Dr. DEVITA. That is the plan that was submitted as part of our master file, yes.

Senator HAWKINS. Did you approve it?

Dr. DEVITA. Yes, but I think it does not specifically prohibit us from reporting the suspected reaction to the FDA. It just sets up a system for investigating suspected reactions. That is why there was some confusion in the interpretation of the document.

Yes, I approved that.

Senator HAWKINS. The chart clearly shows that the adverse reaction form is to be submitted to the FDA, as well as to all investigators receiving the drug. Is not that true?

Dr. DEVITA. Yes, Madam Chairman.

Senator HAWKINS. And that the Adverse Drug Reaction form is to be submitted to the FDA while the classification process is going on.

Dr. DEVITA. That is correct.

Senator HAWKINS. Would you agree that your own rules were as easily violated as the Federal regs?

Dr. DEVITA. I think all rules are violated with equal ease wherever they are promulgated. So, I think we——

Senator HAWKINS. Is not that rather cavalier when we are dealing with human lives?

Dr. DEVITA. No, no, I think that, by the very nature of the very complex field we have, I do not think that our rules will be any more or less violated than any other rules set up. Again, I wish to stress that this was a misunderstanding——

Senator HAWKINS. I would hope they would be less violated. I mean, in your agency they should be less violated than, say, the time we come to work or the time we leave or forms that we fill out for off-time or sick leave or vacations, et cetera. There are so many regulations——

Dr. DEVITA. For a program our size, Madam Chairman, I think that the investigators do a remarkably good job adhering to FDA regulations and adhering to the guidelines that we set up. But it is, again, a program involving 6,500 investigators and 80,000 patients.

I think, if I told you that there will never be a violation of some regulation that we think is very clear at the NCI, I would probably be sitting here before you at some future time explaining why such a violation occurred. The only way we can tighten the program down to the point where there will be no violations ever possible would probably be to stifle it completely with a system that none of us really would desire to implement.

Senator HAWKINS. Our concern is that it is one thing to disseminate the information to the investigators and to all those using the drug. It is another matter if that decision has to be made by you as the director. If you as the director do not understand the regulations, then it never gets disseminated to those that really need it.

Dr. DEVITA. Yes, yes, indeed. Well, I think I understand the regulations quite clearly, Madam Chairman. And the Director of the Division of Cancer Treatment, who is responsible for that program, understands the regulations very clearly. And certainly our staff who operated in the cancer therapy evaluation program understand the regulations very clearly.

Senator HAWKINS. Regarding the now-familiar late reporting case involving the drug methyl-CCNU, you stated last week that you were tardy in reporting and that the investigators were too careful to be sure that the drug did not result in ADRs before sending it to the FDA.

Don't you think that "too careful" is a poor choice of words?

Dr. DEVITA. Our investigators are scientists, Madam Chairman. They like to be 100 percent sure that when they say something is happening that is related to either a positive effect of a drug or a negative effect of a drug, that it is in fact true. Therefore, their general tendency is to analyze data, put it together, and write a publication to be submitted and reviewed in a scientific journal.

I think that, if we do not continually stress to the investigators that such a procedure is acceptable scientifically but not acceptable in reference to regulations, they would be more responsive. Their tendency is to be scholarly and do that.

That is what I meant by being too careful. We have continually reminded them that they can be as scholarly as they want, but they have to tell us of an adverse reaction. And we have to report it to the FDA. And we have to notify our investigators. And then they can go through the——

Senator HAWKINS. In answers to previous questions, however, you just recently, about 5 minutes ago, said you were remiss?

Dr. DEVITA. Well, that is what I meant by——

Senator HAWKINS. Scholarly?

Dr. DEVITA. I think that instead of carefully working up the data without notifying the FDA, we should have carefully worked up the data and notified the FDA. And, therefore, that single step was omitted. In that case I believe we were remiss, yes.

Senator HAWKINS. I believe you used the word careless?

Dr. DEVITA. No. I do not believe I used the word careless. I think we were remiss, and it was a misunderstanding; but we were wrong. We clearly understand that regarding suspected adverse reactions, but remember the emphasis I put before on adverse reactions that do not exist. We are very concerned now because we may be reporting so many adverse reactions that turn out not to be adverse reactions that we can clutter up the system.

So, our investigators are very alert now, but they are also very concerned that they will not be able to distinguish from the various messages they are getting from the Cancer Institute.

Senator **Hawkins**. Could poorly managed be used in regard to this?

Dr. **DeVita**. I do not believe it is an example of poor management at all, Madam Chairman, no. I think it is an example of what I said. Our investigators are scientists, who tend to be scholarly and tend not to think in a regulatory way and therefore will write a paper and submit it to a journal before they notify us, the sponsor, when we have a responsibility to report that effect to the Food and Drug Administration.

We have found this to be the case in a number of the instances of the nitrosoureas. Reports were made and published in journals that are widely read before we were notified. That is not poor management. It is scientists who have approach——

Senator **Hawkins**. Do scientists make good managers, in your opinion?

Dr. **DeVita**. I think some scientists make excellent managers because they are often faced with decisions that have to be made instantaneously with incomplete information. When you translate that into management, it often makes for very decisive management.

Senator **Hawkins**. On Tuesday we heard from two sets of parents, the Palmadessas and the Agostinos. They were not very happy. The Palmadessas, who lost their son Michael to methyl-CCNU chemotherapy, learned for the first time on Tuesday that preclinical tests of methyl-CCNU showed kidney failure in all species of animals that received methyl-CCNU.

Both sets of parents testified that they were not informed as to the possible side-effect of kidney damage. What kind of answer do you have for the Palmadessas?

Dr. **DeVita**. Yes, I mentioned that just previously, Madam Chairman. I think up to 1977 none of our clinical studies showed renal toxicity. Therefore, we were not in a position to inform people that in fact renal toxicity was something they should expect. Now, the animal data——

Senator **Hawkins**. Did you have animal data in seventy——

Dr. **DeVita**. Yes, we had animal data. All the early clinical studies with thousands of patients looked for renal effects in humans based on the animal data. But we know that 50 percent of the renal toxicity that appears in drug studies does not show up in humans. So, that after thousands of patients not seeing renal toxicity, we felt that there really was not a problem of renal toxicity with the nitrosoureas. And we were not informing patients any longer by the time the Palmadessas——

Senator **Hawkins**. How many of the animal species showed renal toxicity?

Dr. **DeVita**. I think that it was clearly apparent in dogs. But in the experiments in dogs or in mice or in monkeys that showed animal toxicity, the renal toxicity was not of the type that would show cumulative toxicity, which is really what happened ultimately with nitrosoureas. It is a cumulative dose effect.

Senator **Hawkins**. From 1972 animal studies in several species had clearly indicated that kidney toxicity progressing to kidney failure was an important side-effect of methyl-CCNU. That is quoting from a 1972 FDA review of a monkey study.

Dr. **DeVita**. Yes, ma'am. But, Madam Chairman, I did the early clinical studies with the nitrosoureas, and we did not see renal toxicity in humans. Again, I should point out that one of the reasons why we assume that drugs are toxic to all organs in the early phases is because the animal tests that we use are not accurate predictors of human organ toxicity.

It is true. I am not trying to say that the animal data did not show renal toxicity. But, after the first phase I and II studies without any renal toxicity in humans, we felt that that was an example of overprediction. And therefore renal toxicity was monitored in patients. All patients had renal functions monitored. But we did not think it was a clinical toxicity.

Therefore, until 1977, when the first case came in that ultimately proved to be renal toxicity, patients were not ordinarily informed that renal failure might be a consequence of exposure to the drug, which accounts for——

Senator **Hawkins**. You did not do that?

Dr. **DeVita**. Beg your pardon?

Senator **Hawkins**. That was not customary?

Dr. **DeVita**. That was not customary because we had not seen it in humans.

Senator **Hawkins**. So, the Palmadessas should not have been informed?

Dr. **DeVita**. If we did not know it existed in the form of chronic renal failure, which we had never seen before, it was not possible for us to tell them of the existence of a toxicity we were not aware of.

Senator **Hawkins**. On Tuesday this subcommittee learned that in January of this year Dr. Finkel of the FDA asked the NCI for a report on the patient deaths attributable to the investigational drug called DCF.

Dr. **DeVita**. Yes.

Senator **Hawkins**. Subsequently, the FDA repeatedly demanded that the NCI produce this report. When did the FDA finally get that report?

Dr. **DeVita**. There were several things that happened there, Madam Chairman. First of all, we asked for an extension of that annual report because it is an extremely complicated drug and we received permission to have an extension for filing that annual report from the Food and Drug Administration. One of the reasons for doing that is the NCI was holding a conference on deoxycoformycin, DCF, to go over all the data. The FDA was invited to and attended that conference and received the minutes of that conference. They received interim reports.

Finally, I believe they received a report within the last couple of weeks for the deoxycoformycin. But we were acting with the understanding of the Food and Drug Administration that we were trying to collect pertinent data and would give them interim reports.

Senator **Hawkins**. Our investigation has demonstrated that, while the agency's highest officials have repeatedly disclaimed any lack of cooperation between the FDA and the NCI, the individuals at the middle levels who we heard from, where the work is actually done, have been denied and frustrated in their efforts.

How can you expect these individuals to do their jobs properly when the relationship between the two agencies is so fragile?

Dr. **DeVita**. Well, let me preface my remarks by just saying something, and then perhaps Dr. Crout would care to comment on that.

We are dealing, again, in a very complicated area. The issue of toxicology is a complicated scientific issue. It is quite unusual to expect that we would get 100 percent unanimity on whether we should or should not use a particular toxicology protocol. So, the fact that we have differences of opinion at different levels in the organization does not come as any surprise.

I counted 187 scientists involved in the discussion of the toxicology protocol. And there were three or four who disagreed with the remainder. As program directors, we tend to go with the weight of scientific evidence. But that always leaves a small number of people who feel their point of view was not given proper weight and attention. And I think that can be interpreted as failure to communicate or lack of cooperation between the agencies.

We certainly do not have unanimity of opinion on the community cancer programs we are setting up. These are very complicated issues.

Senator **Hawkins**. Is patient safety being compromised because of the strained relationship?

Dr. **DeVita**. No. I do not believe it is being compromised.

Senator **Hawkins**. Dr. Brandt, if you have to leave, we will be more than happy to excuse you.

Dr. **Brandt**. No, no, I do not have to leave.

Senator **Hawkins**. Senator Kennedy has not notified me when he will return. We have a note from him that he will submit any written questions to you that he may have. If you would like to be excused, you may.

Dr. **Brandt**. Thank you.

Senator **Hawkins**. This subcommittee held a hearing 6 months ago and addressed the same problems that we are addressing now. Congressional oversight should only have to point the way to the managers of our Federal programs. Your assurances to me on May 21 of this year that the adverse reaction controversy was resolved have left a significant question of credibility. Each time we meet, you tell me you have solved the problems that we are now pointing to.

Will you be back before this subcommittee 6 months from now to explain any difficulties you may have in reporting adverse drug reaction?

Dr. **DeVita**. I think the system for reporting adverse drug reactions is fine. There is nothing wrong with the system.

It reminds me a little bit of when Dr. Brandt was referring to the issue of informed consent. There is a human side of this. The human side of this is the willingness of the investigator at the other end to pick up the telephone and say: I see something that looks like an adverse reaction. That investigator, when he reaches for the phone, worries as to whether he is going to look like he has something or he is going to look like someone who calls the alarm too often. And we are trying to convince them to err on the side of calling us.

So, the human factor is something I cannot predict. If I have anything to say, if I have any influence over my investigators out there, then I am urging them, and they are hearing you, and they are hearing your committee. I think they have gotten the message quite clearly that we want to know about adverse reactions.

I hope we do not have to come back here and explain something that gets to a delayed report.

But can I come back to another one that reminds me again of this issue, and that is Cisplatin. I remember one of our very effective drugs, Cisplatin, was a very controversial drug. It had kidney toxicity to such an extent that it was almost dropped. At the time the kidney toxicity appeared, there was no evidence that it was working because it did not work in colon cancer. It did not work in breast cancer. And it did not work in lung cancer. But it turns out that it is probably the most effective drug in testicular cancer and is responsible for the improvement in survival of people with metastatic testicular cancer from 10 to 70 percent in the past 5 years. Lo and behold, we have learned to handle the renal toxicity. And there was a time when people were not reporting in the sense that they were dealing with the toxicity trying to solve it rather than reporting it. Yet, the end result has been so salutary that I think there is still that human factor out there: when am I seeing something that is unexpected and adverse, or when am I seeing something that is a normal consequence of the use of these very cytotoxic chemicals that clearly are very difficult chemicals to deal with.

Senator HAWKINS. Thank you, Dr. DeVita. Dr. Crout, how long have you been director of the Bureau of Drugs?

Dr. CROUT. Since 1973.

Senator HAWKINS. 1973?

Dr. CROUT. Yes.

Senator HAWKINS. We have a memo dated March 18, 1980, from your deputy, Mr. Jerome Halperin, to the Commissioner and pertaining to the FDA's investigation of methyl-CCNU. May I assume you were aware of this memo at the time of its transmittal?

Dr. CROUT. Yes.

Senator HAWKINS. This memo states, quote:

> During an investigation of a clinical investigator of the anticancer drug CCNU, sponsored by the NCI, we found evidence that NCI may have failed to report, in a timely manner, a serious adverse effect.* * * Because of the sensitivity of the issues and their impact on a sister agency, Dr. Crout planned to call Dr. Vincent DeVita, Acting Director, NCI, in the morning to alert him of the potential adverse publicity, even though it would otherwise be premature to contact him on a regulatory matter before the Bureau has a position and recommendation for action.

[The information referred to follows:]

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : The Commissioner
Through: Acting Deputy Commissioner

DATE: March 18, 1980

FROM : Deputy Director
Bureau of Drugs/HFD-2

SUBJECT: Investigation of NCI Study

During an investigation of a clinical investigator of the anticancer drug CCNU, sponsored by NCI, we have found evidence that NCI may have failed to report, in a timely manner, a serious adverse effect, i.e., renal toxicity. The inspection of Dr. Harvey Cohen at the Sidney Farber Hospital in Boston occurred after the Agency received a complaint from the mother of a child who received the drug and later developed kidney damage. Documents indicate that NCI apparently was informed of the kidney problems in May 1978 but did not report them to FDA until February 1979.

Further details are sketchy as the investigation is still in progress, although the division expects the EIR from the Boston District Office shortly. Until the report has been evaluated, the Bureau will not have a formal recommendation for action, but in view of the sensitivity of the issue, and the likelihood of publicity (described below), we want you to be aware of the situation.

Unrelated, originally, to the CCNU issue, a reporter from the Boston Globe has been investigating the relationships between Boston University, a Dr. Mark Strauss (an oncologist formerly associated with BU) and NCI. It appears that Strauss may have falsified records, violated the protocols, etc., of several studies which he conducted at BU as an investigator for NCI. We have investigated Strauss; the EIR's have just arrived from BOS-DO. We have learned also that NCI may have cut BU off from further studies of investigational cancer drugs since the revelations about Dr. Strauss.

The Globe reporter has interviewed several people from the Bureau, as well as BU and NCI staff and is expected to write an article shortly which will come down hard on NCI for its failure to monitor Dr. Strauss. FDA may come in for criticism too, for allegedly having a double standard in enforcing its regulations i.e., softer on NCI, hard on drug companies. Finally, because the reporter is supposedly a good investigator, has talked with Bureau staffers in the Divisions of Scientific Investigation and Oncology and Radiopharmaceutical Drug Products, and because the CCNU problem came from Boston, it is likely that his exposé will link both of these matters.

Because of the sensitivity of the issues and their impact on a sister agency, Dr. Crout plans to call Dr. Vincent DeVita, Acting Director of NCI, in the morning to alert him of the potential adverse publicity, even though it would otherwise be premature to contact him on a regulatory matter before the Bureau has a position and recommendation for action. Dr. Crout intends to review the above information with Dr. DeVita and suggest that he notify Drs. Fredrickson and Richmond and Secretary Harris of the potential adverse publicity.

If you would like additional information or if you would prefer an alternate course of action, please call.

Jerome A. Halperin
Jerome A. Halperin

cc:
Dr. Novitch
Mr. Hile
Dr. Petricciani
Dr. Crout
Dr. Kelsey

Senator HAWKINS. Would you care to comment on this memo and tell us if you did alert Dr. DeVita?

Dr. CROUT. Yes, I did. We quite naturally have an obligation to notify the Commissioner, the Assistant Secretary, and the Secretary as necessary when there are problems going on within the department that they should know about. So, there are courtesies, notifications that I think are appropriate among Federal agencies, and we did that. Yes; I did call Dr. DeVita the next day.

Senator HAWKINS. Even though it was on a regulatory matter?

Dr. CROUT. No; to notify him that we were—it is my recollection—about to have an investigation. That is not, that is not apart from what I would take to be appropriate protocol among Federal agencies in the same department.

Senator HAWKINS. Dr. Crout, as you know, activity in the FDA's investigation of methyl-CCNU ceased in the summer of 1980. Yet, your notice of adverse findings concerning failure to promptly report life-threatening drug reactions, the inadequacy of patient informed consent, and control over distribution of drugs did not issue until April 6, 1981, which is 10 months later.

Why did that take so long?

Dr. CROUT. I am told our staff delayed sending that letter because there was a secondary issue arising with respect to the performance of the institutional review board at the Cancer Institute and indeed at several of the institutes at NIH. So, in order to give the Cancer Institute a comprehensive listing of troubles, there was—from our perspective—need to wait for an inspection related to the IRB's. And the whole thing was put together into one letter.

[The information referred to follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES · Public Health Service

Food and Drug Administration
Rockville MD 20857

APR - 6 1981

Dr. Vincent T. DeVita, Director
National Cancer Institute
Room 11A-52, NIH 31
National Institutes of Health
Bethesda, Maryland 20014

Re: IND 7681/semustine-methyl CCNU
IND 4595/lomustine-CeeNU
IND 969/carmustine-BiCNU

Dear Dr. DeVita:

I am writing to draw your attention to a problem we have encountered regarding the reporting of adverse reactions to FDA and to the clinical investigators performing Phase I and II studies under the sponsorship of NCI. Our specific concern was precipitated by the finding that neither FDA nor clinical investigators were advised in a timely fashion of renal toxicity in human subjects receiving nitrosoureas. Such a toxicity might have been anticipated in view of the animal findings with BiCNU and Methyl CCNU. In addition we have other concerns about delays in incorporation of the nephrotoxicity in clinical protocols, delays in submission of annual progress reports to FDA, the adequacy of patient informed consent, the reporting of adverse reactions to the institutional review board (IRB) responsible for NCI's intramural studies, as well as continuing review of ongoing studies by the IRB, and control over distribution of investigational drugs.

As you know, representatives of FDA and NCI have met periodically over the past few years to discuss issues of mutual interest regarding the study of anticancer agents and to develop a working relationship between our respective staffs. These meetings led, in part, to publication in the Federal Register on May 1, 1979 of a Memorandum of Understanding Relative to Anticancer Drug Development. In this MOU the Division of Cancer Treatment (DCT) agreed to comply with all applicable laws and regulations pertaining to the sponsorship of investigational drugs for clinical trial. DCT also agreed to maintain with the Bureau of Drugs of the FDA a Master File which is to include DCT's plan for data reporting. DCT has filed such a plan with FDA. This plan includes a detailed flow chart on DCT's mechanism for dealing with adverse reactions when they are reported by investigators, decribes the reporting responsibilities of investigators and also states that the Cancer Therapy Evaluation Program of the DCT is obligated to report any serious adverse reactions to FDA within 15 days.

Detailed below are areas where we feel that some of the commitments made in the MOU and described in the Master File have not been met in the case of the nitrosourea studies. Many of these observations were brought to the attention of Dr. Bono and Dr. Poster of NCI by Dr. Hensley of our Division of Scientific Investigations in a meeting on June 6, 1980 when they were shown pertinent documents and correspondence. We recognize that you may have taken corrective action already in many instances.

A. Requirement for prompt reporting of serious adverse reactions to FDA.

21 CFR 312.1(a)(6) requires that sponsors of investigational new drugs promptly investigate and report to the FDA and to all investigators any findings associated with the use of the drug that may suggest significant hazards, contraindications, side effects, and precautions pertinent to the safety of the drug.

On August 21, 1978 FDA received a complaint from a mother alleging that her child developed kidney failure following treatment of brain tumors with methyl CCNU. She also told us that on August 22, 1974 she signed a consent but was informed of two side effects only, nausea and aplastic anemia. IND 7681 records as of 1978 did not identify renal toxicity in humans as an adverse reaction.

In our follow-up of this complaint we learned that the Investigational Drug Branch (IDB), DCT had been notified as early as November 1, 1977 and several times during 1978 regarding renal abnormalities observed following human use of nitrosoureas (methyl CCNU and BiCNU).

By letter dated November 1, 1977 Dr. H.B. Neustein of Children's Hospital, Los Angeles notified Dr. Andrew Turrisi of the IDB of renal toxicity in a patient treated with BiCNU.

By letter dated May 19, 1978, Dr. Abraham Lieberman of New York's Bellevue Hospital (Baldwin's group) notified Dr. Thomas Strike of the Brain Tumor Study Group (BTSG) of NCI of renal toxicity in four patients treated with methyl CCNU and BiCNU. Dr. Lieberman stated that the purpose of this letter was to notify the BTSG and the FDA to the real dangers of long term chronic therapy with these nitrosoureas. This letter was acknowledged by Dr. Turrisi on June 15, 1978.

In a letter dated November 13, 1978 Dr. Jensen-Akula, IDB, reminded Dr. Richard Fisher, Senior NCI Investigator, Medicine Branch of a previous conversation regarding renal pathology in a patient treated with methyl CCNU at the Clinical Center. This letter also referred to "several reports of nitrosourea induced renal failure" (from Dr. William Harmon of Boston Children's Hospital, Dr. Hagelson of the Medical College of Virginia and Dr. Neustein).

FDA, however, was not officially notified of such an adverse effect until March 2, 1979 in a cover letter from Dr. John Penta, Head, Drug Regulatory Affairs Section, IDB, NCI, to our Division of Oncology and Radiopharmaceutical Drug Products.

B. Requirement for prompt reporting of serious adverse reactions to clinical investigators.

21 CFR 312.1(a)(6) not only requires reporting of adverse findings from IND studies to FDA, but to all investigators There was a considerable delay in the reporting of the renal toxicity to both extramural and intramural investigators. As a result of various inspections conducted by FDA and a review of some IND files we have observed the following situations:

1. Intramural investigators.

Dr. Jensen-Akula in his November 13, 1978 letter to Dr. Richard Fisher stated, "...it does appear that the nitrosoureas have the capacity to induce renal damage if given for a long enough period of time." Distribution of this letter shows a carbon copy directed to "Drug file Me CCNU adverse drug reaction." Thus this official notification to Dr. Fisher occurred about six months after Dr. Lieberman's letter to NCI.

It was not until May 29, 1979, that Dr. Richard Fisher, Medicine Branch, COP/DCT/NCI notified Staff, Medicine Branch, COP/DCT/NCI that "...to date we know that at least one patient treated at this institution has developed chronic renal failure in the absence of other known causes." In this memo, Dr. Fisher detailed specific measures to monitor renal function of study subjects and noted that the consent form for this study will be appropriately modified.

2. Extramural investigators.

Although the Brain Tumor Study Group investigators were apparently sent a copy of Dr. Lieberman's letter on June 7, 1978 it appears that it was not until early 1979 that all methyl CCNU investigators were informed of renal toxicity associated with its use. (A memo from Dr. Jensen-Akula dated February 23, 1979 informed all investigators).

C. Delay in revision of protocols.

There appears to have been a delay in incorporating the findings of renal toxicity into clinical protocols.

Dr. Richard I. Fisher was a principal investigator in clinical research project #76-C-151, "Therapy of Patients with Malignant Melanoma" conducted at NCI. The protocol for this continuing study, approved by the NCI Clinical Research Subpanel on November 27, 1978 mentions that no renal toxicity attributable to methyl CCNU had been observed in man. A status report for this project dated October 18, 1978 states that no new hazards or serious discomforts were experienced and that a literature search disclosed no new hazards relevant to the protocol. In addition, Protocol #2091 (May 2, 1980 revision in IND 4595/CeeNU) for a Northern California Oncology Group (NCOG) study states that renal toxicities have not been a problem of clinical significance in man.

In contrast, an undated Drug Master Sheet (appendix III, page 17) for Southwest Oncology Group study # 7983 states that some cases of mild kidney damage have recently been observed in children, therefore kidney functions should be monitored.

D. Requirement for submittal of annual progress reports to the IND.

21 CFR 312.1(a)(5) requires that the sponsor of an IND submit to the FDA accurate progress reports of investigations and significant findings at reasonable intervals not exceeding one year.

A review of the IND files for numbers 4595 and 969 shows that there have been no annual progress reports since October 20, 1977.

Also, although NCI did not withdraw IND 969 until March 27, 1980, there were no reports of renal toxicity associated with BiCNU treatment in the record.

No progress reports for IND 7681 were filed between October 20, 1977 and March, 1979. A progress report was filed in March, 1979.

E. Informed Consent Requirements.

Section 505(i) of the Food, Drug & Cosmetic Act requires that the clinical investigator obtain the consent of the study subjects. "Consent" is defined in 21 CFR 310.102(h) to include, among other things, the hazards involved.

The consent forms for Dr. Fisher's project #76-C-151, "Therapy of Patients with Malignant Melanoma", approved November 27, 1978, made no reference to the potential risk of renal disease with nitrosourea treatment.

F. Requirement for continuing review of studies by IRB and for reporting of adverse reactions to IRBs.

Assurances that an IRB will conduct reviews at intervals appropriate to the degree of risk, but not exceeding one year, are required by 21 CFR 312.1(a)(2) item 10C. The regulation also requires that the clinical investigator report to the IRB any severe adverse reactions.

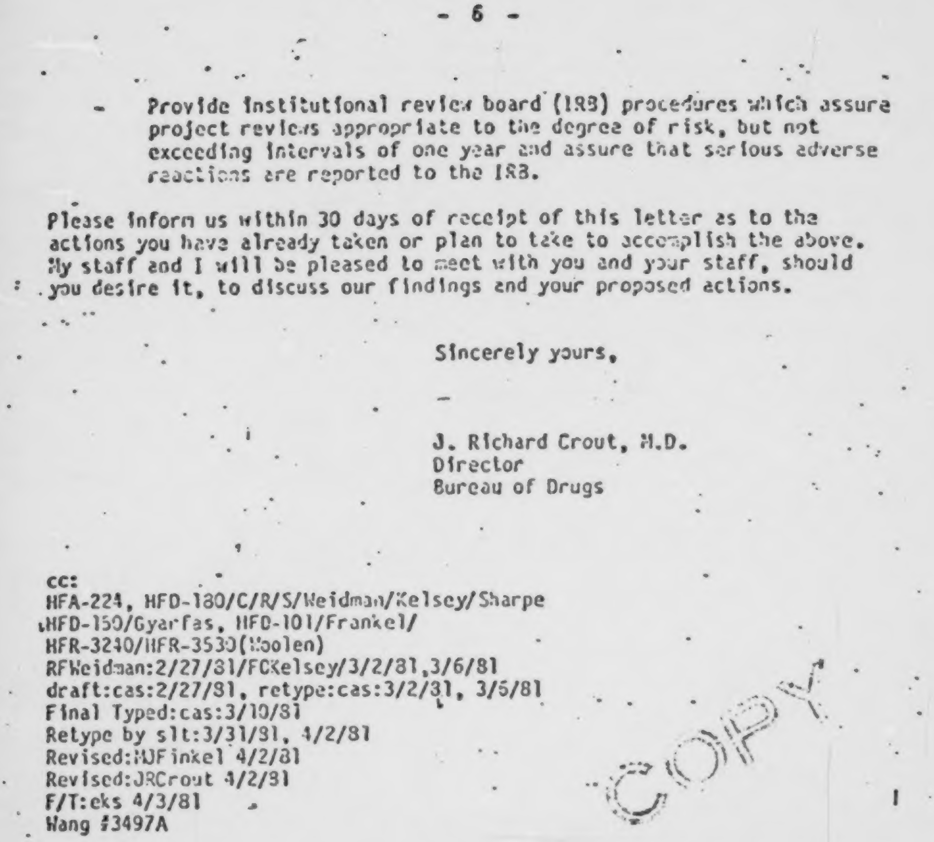
An FDA inspection of the NIH/NCI/Clinical Research Subpanel on November 20, 1930 revealed that adverse reactions were not always reported to the IRB but were reported to the Clinical Director of NCI. This inspection also noted that reviews of ongoing studies are performed by the Clinical Director of NCI, rather than by the IRB, as required by FDA regulations for studies involving investigational drugs.

G. Control over distribution of investigational drugs.

The NCI was apparently unaware that Dr. Jaffe, who was responsible for the treatment of the child whose mother issued the complaint that initiated FDA's review of renal toxicity with methyl CCNU, was using the drug in clinical trials. He had received the drug from an unknown source and apparently was performing a clinical trial outside of an approved protocol. We understand, however, that as of January 24, 1978 NCI has been following written guidelines for the sponsoring and monitoring of INDs which would decrease the likelihood of such a situation in the future.

On the basis of these findings we ask that DCT/NCI take the steps necessary to accomplish the following:

- Review your mechanism for reporting of adverse reactions to all appropriate parties, agencies and clinical investigators to assure that it is functioning in a timely manner in accord with the plan described in NCI's Master File. We recommend that the system be audited periodically to assure that it is meeting its objectives. In addition steps should be taken to assure that new clinical protocols contain all serious adverse reactions previously identified.
- Provide FDA with timely and accurate annual reports for all IND's.



- 6 -

- Provide institutional review board (IRB) procedures which assure project reviews appropriate to the degree of risk, but not exceeding intervals of one year and assure that serious adverse reactions are reported to the IRB.

Please inform us within 30 days of receipt of this letter as to the actions you have already taken or plan to take to accomplish the above. My staff and I will be pleased to meet with you and your staff, should you desire it, to discuss our findings and your proposed actions.

Sincerely yours,

J. Richard Crout, M.D.
Director
Bureau of Drugs

cc:
HFA-224, HFD-130/C/R/S/Weidman/Kelsey/Sharpe
HFD-150/Gyarfas, HFD-101/Frankel/
HFR-3240/HFR-3530(Woolen)
RFWeidman:2/27/81/FOKelsey/3/2/81,3/6/81
draft:cas:2/27/81, retype:cas:3/2/81, 3/5/81
Final Typed:cas:3/10/81
Retype by slt:3/31/81, 4/2/81
Revised:MJFinkel 4/2/81
Revised:JRCrout 4/2/81
F/T:eks 4/3/81
Wang #3497A

COPY

Senator HAWKINS. So, you deferred disseminating information on a life-threatening matter because of an internal matter in the agency?

Dr. CROUT. I think we assumed, and properly so, that the Cancer Institute knew from the original inspection what our concerns were with respect to methyl-CCNU and with their monitoring system. They did not have that officially on the record, but we had—I think they knew, and I think they were, as far as we know, taking steps internally well before the receipt of our letter to correct their system.

Senator HAWKINS. Dr. Crout, I would like to ask you one or two questions about the memo from your deputy, Mr. Halperin, to Dr. M. Finkel. Do you have that letter?

Dr. CROUT. March 24, 1981? Yes.

Senator HAWKINS. Dated March 24, 1981.[1] It concerns the drafting of your notice of adverse findings to the NCI on methyl-CCNU that issued April 6, 1981. Mr. Halperin's memo states:

> We should point out in the notice that we have tried before to bring problems to NCI's attention. We have attempted to impress upon NCI the need to adhere to its obligations as a sponsor and a monitor.

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[1] Memo, dated March 24, 1981 to Marion J. Finkel, M.D., from Deputy Director, Bureau of Drugs, may be found on p. 381.

My reading of this memo is that the FDA had repeatedly warned the NCI in the past of such problems and that your letter of April 6 was a last resort. How do you read that memo, Dr. Crout?

Dr. CROUT. That is not the way we read it. I think we wanted to—I think the purpose of this memorandum was to inform the staff that the whole letter needed some editing. It needed some editing because it was, from our perspective, ambiguous in certain points and it was very bureaucratic in its style. The draft that Mr. Halperin was looking at at this point was, I believe, not acceptable in style written to anybody, the Cancer Institute, a drug firm, anybody. It was just one that we thought was clumsily worded and needed a lot of editing of that sort.

That is the major thrust of his commentary. I think he also wanted to add a point, namely that in the course of our discussions back and forth we had discussed with NCI its monitoring system and that this was an opportunity to reassert our point of view on that. I do not think we felt we were meeting resistance. We simply wanted the record to be straight.

Senator HAWKINS. If you look at the bottom of the last page of your April 6 letter to NCI—do you have that?

Dr. CROUT. I do not have a copy of it with me.

We have got one.

The last paragraph?

Senator HAWKINS. The last, the bottom of the page.

Dr. CROUT. Which page, Madam Chairman?

Senator HAWKINS. Look at the bottom of the last page.

Dr. CROUT. OK.

Senator HAWKINS. You will notice that it apparently had been in preparation and draft since February 27, 1981, a period of more than 2 months. Does it normally take that length of time to draft a letter?

Dr. CROUT. Well, it certainly does when they are sensitive and when they cycle around the bureaucracy with input from a number of people. I think normally that is longer than we desire, but this is not unusual.

Senator HAWKINS. Why is it so sensitive?

Dr. CROUT. I think that once we have had a major investigation of a major activity like the Cancer Institute, it is important that you put your findings together correctly, accurately, and state it well. I do not think it is the only sensitive thing we handle. We handle a number of inspections that are like that. We would treat them the same and do treat occasional major investigations of drug firms in the same way. It is not an everyday occurrence to have a letter like this going to another Federal agency.

Senator HAWKINS. On Tuesday this week Dr. Hensley, the physician who investigated the NCI's handling of methyl-CCNU, stated that, while he was in the process of developing the case, bureau management—which, I assume, is your office—directed Dr. Hensley's superior to provide the NCI copies of everything Dr. Hensley had collected. Did your office give such direction and if so, do you think it was appropriate?

Dr. CROUT. I have been unable to verify the circumstances of that incident, partly because the alleged conversation that would have occurred would have been between myself and Dr. Kelsey, who is the director of that division. And she is out of the country. So, we have not been able to communicate between today and your hearing of 3 days ago.

It is perfectly possible that I said to our staff, to Dr. Kelsey: Please be as open as possible; tell them everything you can and be cooperative. It is a message that I commonly give around the institution and am perfectly comfortable with.

I am very surprised if someone took it as a request for impropriety in the sense of giving somebody under investigation information he should not have. There was absolutely none of that. Indeed, when the staff talked it over, I think they gave to the Cancer Institute what they thought they could and retained what they thought was proper for an investigation without disclosing it.

Senator **Hawkins**. Dr. Wood, a supervisory chemist for the Bureau of Drugs, testified Tuesday: "There is extraordinary pressure at the present time to compromise scientific reviews, to force people to delete deficiencies that are essential for the establishment of good drug quality."

What is your comment on Dr. Wood's statement?

Dr. **Crout**. I was concerned to hear that. I met with Dr. Wood and with her supervisors yesterday about it. It is true that she has come under a good deal of pressure from her immediate supervisors about the reviews in her group of chemists, but I think the wrong implication was given on the reasons for that.

She has come under a good deal of criticism, not only with respect to cancer drugs, because she handles some other areas of drugs, for delays and what are perceived unreasonableness in the reviews out of that group. She has got the biggest backlog of any of our chemists and an average of four times as many complaints of deficiencies. So, her supervisors feel that that group has not been performing well in terms of either the——

Senator **Hawkins**. What was said in your meeting with her yesterday?

Dr. **Crout**. Backlog or the amount of—or their quality. So, that is what is happening. She is coming under that kind of pressure to improve——

Senator **Hawkins**. And is that what was discussed yesterday?

Dr. **Crout**. That is what we discussed yesterday.

I think she would be very hard-pressed to document that the pressure relates to compromising science. The pressure relates to getting the work done in a reasonable way.

Senator **Hawkins**. Were you critical of her yesterday in your meeting with her?

Dr. **Crout**. Yes. She is quite—she understands the criticism she is under.

Senator **Hawkins**. I said were you critical of her testimony yesterday?

Dr. **Crout**. Was I critical of her? I said I thought the press accounts of it—I do not know her exact testimony. The way it was stated in the press was not a correct interpretation of my understanding of the situation. And, I told her that if asked the question that you are asking me, I in no way could support her point of view.

Senator HAWKINS. Would she have felt intimidated in the meeting with you after appearing before our committee?

Dr. CROUT. I'm sorry? Would she have felt intimidated when—I suppose, if she and I had had the conversation prior to her testimony, she might have. But it is not my custom and I have never met with our employees who are about to testify before Congress to urge them on their testimony.

Senator HAWKINS. There was some concern by witnesses that came here that they may be intimidated by their superiors when they return. Would she have felt that way after meeting with you yesterday?

Dr. CROUT. She may have. I think she has got to stand responsible for a statement that in my judgment is incorrect or gave a wrong impression.

Senator HAWKINS. We have an affidavit here which indicates that she not only may feel that way but does feel that way.

Senator KENNEDY. If Madam Chairman would yield.

Are you telling me that you relied on the account in the newspaper rather than taking, reading through her direct testimony as the basis for your conversation with her?

Dr. CROUT. That is all I had yesterday.

Senator KENNEDY. Well, don't you think as a responsible person in the agency that she is entitled to have her direct testimony read——

Dr. CROUT. Oh, she——

Senator KENNEDY [continuing]. In terms of any exchange——

Dr. CROUT. Of course——

Senator KENNEDY [continuing]. With her? That seems to me to be extraordinary procedure, where you take what is allegedly reported in the newspaper, when you are going to talk to an employee. It seems to me that an individual is entitled to have whatever they have stated before this committee reviewed by their superiors for accuracy. And, if there is a difference in it—and I am not particularly familiar with what her work report is, but I do think that any individual who is going to be addressed in terms of their testimony is entitled to have their superiors rely on the direct testimony and not newspaper reports.

Dr. CROUT. I would agree with that. Yesterday——

Senator KENNEDY. Then why didn't you do it?

Dr. CROUT. She gave statements that are reported in the newspaper on Wednesday, and I know very well I am going to have to deal with the problem today. The conversation we——

Senator KENNEDY. Did you try to get a transcript of the hearing?

Dr. CROUT. Yes. I listened to a tape of part of it which was not very legible.

But let me say, the conversation with Dr. Wood yesterday was not an uncomfortable one for her or for me——

Senator KENNEDY. I am just——

Dr. CROUT [continuing]. And the facts were not at issue. She is not——

Senator KENNEDY. The only point is that I do think that people, if they are going to be commented on by others in the Agency, are entitled to have their direct testimony used and not newspaper reports used. I think just a basic fairness and equity entitles it.

Dr. **Crout**. I would agree, but I also think you have got to have—there is no communication gap nor hostility nor discomfort between me, Dr. Wood, nor the people who were here. I have talked with several of them both before and after the hearings and——

Senator **Kennedy**. How many individuals——

Dr. **Crout**. I feel perfectly comfortable having a conversation that begins with: Look, I read this in the newspaper yesterday; what is going on? Now, I do not believe that that kind of communication can be precluded among people who are asked to work effectively together.

I would urge you not to make an intimidation or a kind of a——

Senator **Hawkins**. Did you ask her that?

Dr. **Crout** [continuing]. Is comfort or a problem that is of that type.

If people are differing on their opinions, you have to sit down and talk it over.

Senator **Hawkins**. I want to tell you that she felt very intimidated and called my staff last night at 10 o'clock. We have an affidavit stating that she does feel that she was being intimidated.

[The information referred to follows:]

PREPARED STATEMENT OF REBECCA H. WOOD

Before me personally appeared Rebecca H. Wood, Ph.D., who first being duly sworn, deposes and says:

At about 8:30 a.m. on Thursday, November 5, 1981 I was called by Dr. Crout's secretary and was asked if I could meet with Dr. Crout around 2 p.m. that afternoon. She wasn't positive about the time but it would be after 2 p.m. since Dr. Crout had another meeting until that time. I indicated that I would cancel a dental appointment at 3 p.m. in order to be free that afternoon. Around 2 p.m. Dr. Crout's secretary again called and asked if I could meet now with Dr. Crout. I said "yes" and said I would be there immediately.

I arrived at Dr. Crout's conference room within a few minutes to find the meeting in progress. In attendance were: Dr. Crout, Dr. Finkel, Dr. Kumkumian, Dr. Gyarfas, Dr. Jerussi, and myself.

I asked if a record were going to be kept of the meeting and Dr. Crout responded that none would be kept and that the meeting was only to prepare a response for the hearing on November 6.

Dr. Crout: Dr. Crout was trying to determine the "paper trail", starting from the memo of April 25, 1978 from the Asst. Assoc. Director (Dr. Kumkumian) to the Assoc. Director for New Drug Evaluation (Dr. Finkel) concerning NCI's IND's and the "over requesting" of information by Dr. Wood. Dr. Crout indicated that this memo apparently came about because of the letter of April 13, 1978 from Dr. DeVita (NCI) to Dr. Crout, complaining about letters received from the FDA on IND's 13,952 and 13,953. Dr. Crout asked what action was taken on these 2 IND letters. Did Dr. Gyarfas call NCI and retract them?

Dr. Wood: Dr. Wood indicated that there was no action on these 2 IND's but that 2 subsequent IND letters (IND's 16-505(DCF) and 16-707 (AZQ)) were retracted by FDA.

Dr. Gyarfas: I looked in my file but I couldn't find any memo.

Dr. Wood: Provided Dr. Crout with a copy of the November 30, 1979 telephone memo written by Dr. Gyarfas [in which it is stated that he called Dr. V. Bono (NCI) about IND's 16-505 and 16-707 and informed him that the letters are being retracted and will be modified, stating that the present letters include requests that are far more than required for IND's in phase 1 and/or 2.]

Dr. Crout: Asked what changes were made in the letters. Dr. Kumkumian did not recall what had been done.

Dr. Wood: Provided Dr. Crout with a copy of Dr. Kumkumian's hand-written notes on what changes were to be made in the two letters (filed in jacket).

Dr. Kumkumian: indicated that there were changes made in the timeframes for the submission of requested information.

Dr. Wood: indicated that deletions were also made in some of the requested information. No one asked what was deleted.

Dr. Crout: asked if this procedure (clearance of letters through Dr. Kumkumian) was still being followed. Dr. Kumkumian indicated that he had not seen any NCI letters recently.

Dr. Jerussi: stated that since he has been Deputy Director he has signed off on all IND letters containing chemistry comments and that he didn't know until now that NCI letters were supposed to go to Dr. Kumkumian for review.

Dr. Wood: asked if there had been a memo which recinded Dr. Kumkumian's instructions concerning NCI letters. There was no response to this question.

Dr. Crout: Asked Dr. Wood if she had seen the Associated Press news release, handing her a copy. Dr. Wood said yes and commented that the statements in the Washington Post concerning what she said at the hearing were not accurate. Concerning the AP news release, Dr. Wood said she did not recall saying that we were under pressure to "approve everything as fast as possible", at least not exactly in those words, but that the rest of the news release was fairly accurate. Dr. Wood also said that half of what she said was omitted, such as the statement that we all want to get good drugs out to the public fast but that there were other ways to accomplish this, e.g., streamlining the processing of documents, getting letters out faster, calling up firms to inform them of problems.

Dr. Finkel: indicated that there did seem to be a problem in getting documents to the reviewers in a timely manner.

Dr. Wood: emphasized to Dr. Crout that she had been subpoenaed to appear as a witness and that she did not volunteer, that she was a reluctant witness and had stated this at the hearing, that she did not know specifically what the questions would be since the original topic had been removed from the agenda, and finally that she was under oath to tell the truth and what was said were simply her feelings at that time.

Dr. Crout: acknowledged what Dr. Wood said. He asked Dr. Wood what was meant by the "extraordinary pressure" being exerted at the FDA.

Dr. Wood: Dr. Wood pointed out that the AP news release had restricted this "pressure" to investigational anti-cancer drugs and she stated that it is well-documented that recommendations by the chemists in their reviews were revised or deleted in the case of the 2 IND letters to NCI and the policy of having letters to NCI cleared by Dr. Kumkumian constituted pressure on scientific reviews. Dr. Wood attempted to bring up the subject of the NCI IND for homoherringtonine and how the IND study began with minimal information provided on the drug, but she was not permitted to expand on this.

Dr. Crout: Told Dr. Wood that she had a reputation,not only with NCI but also with industry, for asking for much more information from applicants and sponsors than any of the other Divisions in NDE. Dr. Crout stated that he also knew this personally through Dr. Wood's handling of the NCI IND (IND 16-013) for Laetrile (D-amygdalin) in which her requests for information were excessive.

Dr. Wood: Commented that there seemed to be only a "bean count" being made, i.e., only a count of the number of deficiencies in HFD-150 letters versus that in other Divisions. There was no examination of the validity of the questions and information requested, i.e., the scientific soundness and importance of the requests in assuring drug quality. Dr. Wood suggested that an impartial outside chemist look at noted chemistry deficiencies and assess their validity and necessity.

Dr. Crout: Stated that he might have some concern about this, since he is a physician and not a chemist, but with Dr. Jerussi, a chemist, in the Division there should not be a problem here.

Dr. Wood: Indicated that Dr. Jerussi, as Deputy Director, has goals that are now different from those he had as Supervisory Chemist.

Dr. Jerussi: agreed that he now has different goals. Dr. Crout also agreed on this. Dr. Jerussi indicated that he was considered to be a "tough" supervisory chemist but he had never seen anything like the chemistry letters coming out of HFD-150.

Dr. Wood: indicated that there was considerable difference between the large volume parenterals NDA's in HFD-160 and the many highly complex oncologic drugs, the radiopharmaceuticals, and the anti-inflammatory drugs in HFD-150. The comment caused considerable consternation. Dr. Jerussi was highly indignant. Dr. Kumkumian said "a drug is a drug is a drug". Dr. Wood asked why the six highly qualified chemists in HFD-150 generally are in the same ballpark when it comes to the amount of information requested for NDA's.

Dr. Jerussi: Stated that the reason for this was because Dr. Wood had trained them that way. Dr. Wood was not sure this was the reason.

Dr. Jerussi: brought up the problem of HFD-150 chemists requesting "batch records" and indicated how he had instructed the chemists to stop asking for this in NDA's but that they still persisted and he kept getting opposing memos.

Dr. Crout: Asked Dr. Wood if she was aware what the other Divisions were requesting with respect to batch records.

Dr. Wood: Said that she had discussed the matter with Dr. Casola and he had indicated that his chemists asked for this information.

Dr. Kumkumian: Stated that he had met with the supervisory chemists and told them not to ask for batch records.

Dr. Wood: Stated that information on how the drug was manufactured was essential information for the chemists to have to assure drug quality. She said that it had been agreed with Dr. Kumkumian that this information was needed in applications and could be requested as long as we did not call it a "Batch Record" or "Master Production Record".

She said that she had asked the HFD-150 chemists to comply with this policy and thought there were no further problems.

Dr. Jerussi: Indicated that the HFD-150 chemists have an "adversarial" relationship with industry and that they request "batch records" so that they can check each step and say "got ya" to the applicant when there is a slight difference. Dr. Wood denied any adversarial relationship and said that there concern was a scientific evaluation and that was all. Dr. Jerussi said he had a request for a batch record that almost slipped through him.

Dr. Crout: Asked Dr. Wood if the requesting of information on how the drug was manufactured simply an "end run" around "batch records". Dr. Wood was speechless.

Dr. Finkel: Stated that Dr. Wood seems to be implying that the chemists in the other Divisions are not doing their job, but this does not seem to be the case.

Dr. Jerussi: Stated that he intends bringing the HFD-150 chemists in line. They are now far out field and he intends to bring them in line with the other Divisions.

Dr. Wood: Again asked that the deficiencies be examined for their validity rather than simply the numbers counted. Dr. Wood pointed out that a request for validation of a silver ion method by one of the chemists that was scoffed at by Dr. Jerussi but as it turned out, the test failed for the particular drug. A similar failure occurred in the case of an LAL test. Dr. Jerussi questioned a request for validation of a pH method.

Dr. Crout: Asked Dr. Wood what she would do if she was instructed by Dr. Kumkumian concerning policy on requesting certain information.

Dr. Wood: Stated that hopefully such a policy statement would be in writing and that such policy would be followed completely.

Dr. Finkel: Stated that such instructions do not have to be put in writing by Dr. Kumkumian.

Dr. Wood: suppose I receive such instructions concerning policy on chemistry deficiencies from Dr. Jerussi....

Dr. Jerussi: "That's the trouble!" Dr. Wood does not know who her supervisor is! I am her supervisor and Dr. Gyarfas is her supervisor.

Dr. Crout: "Yes, that's right." If Dr. Jerussi asks you to follow a certain policy you are to follow these instructions.

Dr. Wood: Am I expected to ask the chemists to change their reviews accordingly.

Dr. Finkel: Oh no! They can put a memo in the file.

Dr. Wood: "Oh" (puzzled.)

Dr. Jerussi: I have instructed Dr. Wood to do something about the deficiencies in letters but she has done nothing about it. I have also had 2 meetings with the chemists in HFD-150 and told them that they were asking for too much information and that the number of deficiencies in letters was greatest for HFD-150.

Dr. Wood: I am sorry to have to lay it all out now, but I guess it is necessary. The chemists in HFD-150 have been receiving direct instructions from Dr. Jerussi concerning their work without my being informed at all. Concerning the two meetings with the chemists, I was not invited or informed of what transpired.
The chemists have been asking me if they have two supervisors.

Dr. Crout: Agreed that this was not a good procedure.
Dr. Jerussi: Admitted that this had occurred in a "few" cases. About the meeting, though, Dr. Wood was on detail (in the same office) during this time. Furthermore, the Acting Supervisors were more cooperative than Dr. Wood.
Dr. Jerussi: Said he had trouble communicating with Dr. Wood and, in fact, she had written on the bottom of one of his memos "This problem could have been solved by a 10 second discussion." Dr. Jerussi stated that he was the Deputy Director of the Division and she was not supposed write on his memos.
Dr. Wood: Stated that this event had nothing to do with what was being discussed, it seemed, and thought that it might better be discussed with the particular documents on hand.
The meeting ended at about 3:10 p.m.
Dr. Crout: stated in summary that there was indeed pressure being exerted (on the supervisory chemist) and that this was not out of line. He suggested that there be a training program to get the HFD-150 chemists in line with the other chemists in NDE. Dr. Jerussi volunteered to orgainze such a training program.

Rebecca H. Wood
Rebecca H. Wood, Ph.D.

Subscribed and sworn to by the said Rebecca H. Wood, Ph.D. before me this 5th day of November, 1981.

My Commission expires July 1, 1982

Senator **Hawkins**. We received testimony from six of the FDA employees last Tuesday. They were all under oath. As their superior, do you have any feelings or impressions? Or did you get them all out of the newspaper?

Dr. **Crout**. I guess I do not know how to answer your question. What would you have thought was a reasonable approach for a person who knows these people, is on first-name basis—we work together every day—to say in helping me get ready for this hearing? And I sat down with Dr. Wood and said: What is your point of view; I want to know this for a hearing tomorrow.

I am sorry I——

Senator **Hawkins**. You are her boss, right?

Dr. **Crout** [continuing]. Cannot think of an alternate or a more comfortable or a more human way of dealing with the situation.

Senator **Kennedy**. Thank you, Madam Chairman, for accommodating me.

If I could come back to Dr. Brandt. I think it is important, given the attention both these hearings have received that we hear from the principal responsible individuals within governmental agencies that have primary responsibility over the whole development of cancer policies.

Thousands of patients in this country are receiving cancer therapy. They are worried about the kinds of things they are reading about the cancer program. Scores of parents have written to me. I have had direct communication with a number.

What can you say to those patients and their families today? Is cancer chemotherapy in the United States basically sound, basically well-managed, efficiently done, and properly monitored? Dr. Brandt?

Dr. **Brandt**. I think there is little question that the cancer chemotherapy that is available in the United States is basically sound. I think at the same time, particularly those drugs that are out commercially available, there is very little question about.

I think in our drug development program that we have a framework that allows us to develop those in a sound fashion and in a way that will permit us to identify those drugs that are likely to have good effects. I think there is very little question, and this testimony this morning and testimony last Tuesday and other accounts have demonstrated that there have been some slips; and I think that is true.

Senator **Kennedy**. That is the point I want to get to, the failure to report the side-effects of patients themselves; the failure to obtain informed consent; and the failure of clinical researchers to report adverse side-effects. Is that the exception, or is that the rule in the cancer program today?

Dr. **Brandt**. In the first place, to go to the informed consent, I think there is no question that that is the exception. The failures are clearly the exception. Assuming that you——

Senator **Kennedy**. What exactly is the exception?

Dr. **Brandt**. The failure to obtain adequate informed consent.

I think at the same time, though, Senator Kennedy, that one has to admit that a patient with cancer who, in fact, is faced with virtually a last-resort opportunity, that our concept of what informed consent is, that I might give, for example, I think is probably different than that of the patient. I have been blessed by never having to face that situation, but I think it must be difficult to apply the same standards of informed consent or that is to think that every patient with cancer who agrees to cancer chemotherapy is in fact giving the same degree of informed consent that other people would give under other circumstances.

But I think, given that caveat, that the failure to obtain proper informed consent by clinical investigators is unusual.

The failure to report adverse drug reactions, I think, is in part a matter of interpretation. Adverse drug reactions are very often only known in hindsight.

I might just point out that a very common drug in our society known as aspirin, that I went clear through medical school and through residency and was out taking care of patients for some 10 years before it became clear that gastrointestinal bleeding could be associated with the administration of aspirin. If you look back with hindsight at the evidence, it was clear that it was there; but nobody recognized it.

So, I think that there are going to be instances where our clinical investigators are not going to report what subsequently turns out to be an adverse drug reaction because they do not recognize it as an adverse drug reaction.

Senator **Kennedy**. I think that is probably a fair enough statement. I think what the concern of this committee has been is adverse effects which are significantly more serious in terms of——

Dr. **Brandt**. Yes.

Senator **Kennedy**. Obviously we are not talking about the general practitioners dealing with aspirin in everyday use, we are talking about very highly toxic drugs that are being administered under clinical conditions where we do see adverse effects.

Do you and Dr. DeVita think that we can strengthen that whole program in terms of reporting of these adverse drug reactions? I think all of us are mindful that even after they are reported they are going to be subject to subjective review. But can we develop a process and system that will be tighter in terms of reporting of adverse drug reactions? Are you going to help us see that that is done?

Dr. **Brandt**. Yes, sir. There is no question that we are at the present time focusing a great deal of attention on getting our clinical investigators to report those adverse drug reactions. We will continue those efforts. I think that we will in fact cut that failure down as close to zero as is humanly possible.

Senator **Kennedy**. And that the physicians themselves are going to be notified about them?

Dr. **Brandt**. Yes, sir.

Senator **Kennedy**. Has the cancer institute, Dr. DeVita, withheld adverse reactions from the FDA?

Dr. **DeVita**. Not purposely, Senator Kennedy. I think the methyl-CCNU issue that we have discussed——

Senator **Kennedy**. Well, whether it is purposely or not purposely, we will let others get into that particular issue. But the question is, how can we be sure that it is not going to happen in the future?

Dr. DeVita. Well, I think we have clarified that situation considerably. Our investigators now know that we are to be informed of suspected adverse reactions. And our staff know that they are to report them within 15 days to the Food and Drug Administration, and there is no question about that.

I think Dr. Brandt put it very well. There are two problems with cancer drugs that are even more serious in terms of recognizing adverse reactions than you see with normal other drugs like aspirin and digitalis. One is that many of the reactions that we see that would be considered adverse for aspirin are expected. For example, blood count depressions and so forth are routine concomitants of the use of anticancer drugs. So, we do not report them as adverse reactions. Routine elevations of liver function parameters occur in patients who have had prior chemotherapy, and they are not adverse reactions immediately.

The other is the gray area of hindsight. Something happens. We all look at the data. None of us see an adverse reaction, but later we do. And then when we come back, we find out that it was there a year or so before. So, with the benefit of hindsight, it is often clear that we could have reported an adverse reaction sooner. We are often sitting together, side by side with our FDA colleagues looking at the same data, and do not see it as an adverse reaction.

I think the system is as good now as it can be. The human factor is the one that we were discussing just before you came in with Senator Hawkins. We must continue to remind our investigators, although they tend to want to be scholarly and write papers about an adverse reaction, that the first responsibility is to call us and then write their paper.

I think we have come a long way. I think the attention this subcommittee has given the issue of adverse reaction makes it very useful for our staff because they can now go back to the investigators and say that you see now that this is a serious issue, that we need your cooperation. All the readings I get from the community suggest that we will be seeing far fewer examples.

Now, we do have an example, however, of overreporting adverse reactions, but we are willing to accept that. I gave the example of leukemia that was apparently noted with methyl-CCNU. We report it as an adverse reaction. It turns out that patients with the particular disease it was being used in turn out to get that disease more frequently and it just looked like there was one. But I do not think it is unreasonable to warn people that they might get an adverse reaction and later go back and tell them that it was an overwarning, although these people are generally very anxious anyhow and this does increase their level of anxiety.

Senator Kennedy. Do you think there ought to be special rules for testing cancer drugs, different from testing antibiotics, for example?

Dr. DeVita. I believe the point that Dr. Crout made, that phase I testing in cancer drugs is unique in the sense that we always use them in people who have the disease and who desperately need it, is a point of consideration. However, we have been asked in the past whether we think we should regulate our own distribution of anticancer drugs, in other words we should be our own FDA. I do not believe that any of our staff feel like that responsibility should be taken from the FDA. We prefer not to regulate. We prefer to be responsible for the research and development of these compounds.

Senator **Kennedy**. The question was more related to the testing of cancer drugs, whether you think there should be a different——

Dr. **DeVita**. I think the urgency is different than in many other diseases. I am in favor——

Senator **Kennedy**. The urgency is different. But is the answer yes or no? I know the urgency is different.

Dr. **DeVita**. The answer is yes, if special consideration can be given to the fact that phase I testing in cancer drugs should be accelerated, not decelerated, because of the desperate need in this population. I think that we have been doing that——

Senator **Kennedy**. Whatever change that you are talking about, would come about you want to be careful that the change does not make it more difficult.

Dr. **DeVita**. That is correct.

By the way, Senator Kennedy, I think that the master file we developed with the Food and Drug Administration in 1976, and the monitoring system that we set up, and the drug distribution system that we also set up in 1976 accelerated the testing of cancer drugs in phase I. I think that was a very positive step. So, I do not really see a need for a regulatory change on that.

Senator **Kennedy**. How many employees are involved in the monitoring in the experimental cancer drug testing program?

Dr. **DeVita**. Well, our employees at the Cancer Therapy Evaluation Program, which is the staff that manage the entire clinical testing program, now number 38. That was a tripling since 1974. There are four people who are specifically referred to as monitors in that particular program.

Senator **Kennedy**. Are more needed to do an adequate job?

Dr. **DeVita**. We are setting up some additional requirements that will require more monitors. And we will provide them. We think the figure that is probably reasonable for all the additional requirements in the system that Dr. Brandt described in his testimony will be about nine. And we will provide those staff to the——

Senator **Kennedy**. Would you let us know? Will you inform this committee when you finally make that judgment?

Dr. **DeVita**. Certainly.

Senator **Kennedy**. And whether you need additional resources for that particular program.

Dr. **DeVita**. Well, we are a large institution, Senator Kennedy. We are at the present time going through our positions one by one, reallocating resources amongst the whole variety of programs. Actually, the drug development program is only a small part of the entire Cancer Institute.

Senator **Kennedy**. If there are additional resources necessary to do this job, I think we want to hear about it. I do.

Dr. Brandt, the President's commission, in its testimony to be given here today, states that nothing has been done in the past 3 years by your Department to implement the 1978 recommendations for routine site visits, audits, and assistance to IRB's, and sanctions for investigators and institutions.

Why has the Department not followed these recommendations?

Dr. **Brandt**. I think the Department—we feel like we have followed those recommendations. I heard that—well, with one exception, I guess to the general recommendations, and that is the feeling by the President's commission that onsite visits and that kind of monitoring of the IRB's is required. That is a position that we are not prepared to accept at the present time.

I have been having a fairly detailed review of that study comparing it to the new regulations which went into force in July 1981 to try to determine precisely what the—recommendation by recommendation to determine precisely where we may be differing.

Senator **Kennedy**. Why does the President's commission say that it has not been done? You say that it effectively has been done.

Dr. **Brandt**. I do not know, sir. I do not know, sir.

Senator **Kennedy**. You agree that they have not done the site visits?

Dr. **Brandt**. That is correct. We——

Senator **Kennedy**. Why have not they done the site visits? Is not there a possibility that some of the problems that we have heard talked about today might not have existed if they had been done?

Dr. **Brandt**. We have two sets of regulations concerning that, that is within the Public Health Service. One are those by the NIH, which operates under a general assurance activity, where the institution provides us with assurances concerning the type of IRB they are putting together, the kind of people on it, and their processes and procedures. Furthermore, at the NIH, should any study section in their evaluation of grant requests request information concerning that IRB, then they are in fact eligible to get it.

The FDA, on the other hand, does site visit IRB's and does in fact do analyses of them——

Senator **Kennedy**. On that point, Dr. Crout, as I understand, the commission found similar problems with recent FDA inspections according to the testimony of the commission. Do you have any comment on that?

Dr. **Brandt**. You mean found deficiencies in the IRB——

Senator **Kennedy**. No, I am talking about site visits. The particular one I guess they are talking about is M. D. Anderson. It is in their testimony, as I understand. I am just wondering whether you want to comment on that while you are up here. We will hear that mentioned by them, and I just want to give you a chance to respond.

Dr. **Crout**. I guess I would like to have the question clarified, sir.

Senator **Kennedy**. Well, we will get the direct testimony. If you are not here, I will ask for a response in a letter and make it a part of the record if that is all right, Madam Chairman.

Senator **Hawkins**. Surely.

Senator **Kennedy**. Thank you very much.

Senator **Hawkins**. Dr. Crout, it seems apparent to me that the relationship and communications between your personnel and that of NCI continue to be "strained", as Dr. Hensley put it. What do you think the solution to this problem is?

Dr. **Crout**. I suspect we will keep working at it. We have been working at it for several years, and we will continue. As both Dr. DeVita and I learned about our own institutions from hearings like this—and it is clear to me there are some communication problems within our institution—it is clear that the meetings between the two institutions at management levels and including the staff have not been held as frequently as they ought to. And I think we will redouble our efforts in that regard.

I cannot think of a specific system change. These are people problems we will keep working on.

Senator **HAWKINS**. Do you think the paper prepared by the NCI called the "Evolution of the National Cancer Institute Master Plan for Drug Development and Interactions with the Food and Drug Administration" has served to relieve the strained relationship?

Dr. **CROUT**. No; that is an unfortunate document, and I think that is so recognized by both Dr. DeVita and me. It has not gotten wide circulation, or publicity, or commentary, as far as I know. We have tried to, both of us, take a cool it attitude and have it go away.

Dr. **DEVITA**. Madam Chairman, if I may, I can explain the origins of that document. It is a continual problem for the Cancer Institute to find and employ very high quality clinical investigators to be responsible for the cancer therapy evaluation program. We are not as competitive in salary structure, and these people would rather be out there on the front doing the investigations themselves. We hire very good people. We are very proud of our staff. But, if you look at our current staff, the Associate Director all the current branch chiefs, and all the current monitors are all new.

I think that document was really just prepared to give them some corporate memory. It explains how we evolved between 1974 when the NCI and the FDA both agreed that very sizable changes were needed in our system to reduce the tensions between the two institutions. At the present time, I think the tensions are as low as you are likely to see, frankly, in an institution that is regulated by another institution.

Senator **HAWKINS**. Did you approve of this document?

Dr. **DEVITA**. I think so in the sense that it provides the corporate memory for people so they do not stumble and make a mistake, again—in other words, we do not want to have tensions between the FDA. We want them to understand how the systems have evolved. To the extent that it provides that kind of information. It does not represent the FDA's point of view. To the extent that it is personally critical of anybody, I think, I do not think it should be—it need not have been put on paper. It could have been done verbally. It was an innocent purpose, I think, and not a malicious one. When you have staff that are all brand new, having to handle complicated problems, you want to make sure they are always up to speed on what is happening. An institution our size requires the installation of corporate memory in new people. It is a very complicated program for someone to come in and understand and adapt to very quickly.

Senator **HAWKINS**. Am I correct in assuming, Dr. Crout, that, following the subcommittee's hearing on Tuesday, that you were made aware of the written response from the Bureau of Drugs to Mr. Palmadessa on June 17, 1981?

Dr. **CROUT**. Yes.

Senator **HAWKINS**. During their testimony, Mr. and Mrs. Palmadessa left no doubt in anyone's mind that they were very disturbed over having received from the FDA the boilerplate brochure entitled "Clinical Testing for Safe and Effective Drugs." They had written a letter, which you have been handed, to the FDA asking for information on methyl-CCNU, the drug that their 14-year-old son had been given prior to his death from kidney failure.[7]

Do you think they have reason to be disturbed? What changes have you made, if any, regarding responses made by the FDA?

Dr. CROUT. I apologize for the letter. I am writing a letter to both the Palmadessas and to the Agostinos. I hope that will at least correct this immediate insensitive response that they got before.

Again, I do not think there is anything wrong with the system. I think that we are just going to have to heighten the sensitivities of people who write these to recognize when a reply is sometimes too bureaucratic or not forthcoming. I do not think we have a system problem. I think we have a heightening of sensitivity issue.

Senator HAWKINS. What about amending the problem?

Dr. CROUT. Amending?

Senator HAWKINS. The problem that you had. A management problem, excuse me.

Dr. CROUT. I am not——

Senator HAWKINS. You do not think you have a management problem if you get a letter to the FDA from a parent who stated in the letter that their son was stricken with a malignant brain tumor, was given methyl-CCNU, and were not advised that this drug could cause kidney failure? It is very specific, pertinent question that they had——

Dr. CROUT. I agree with that. It was not well answered but——

Senator HAWKINS [continuing]. And they got the boilerplate response.

Dr. CROUT [continuing]. I do not believe we have a system or a management problem. We have a—the person who got it to answer did not consult widely enough and draft a very good answer. That is what happened.

Senator HAWKINS. Do you get very many letters like this?

Dr. CROUT. Lots of them. I mean, we get a lot of letters. I suspect there are others out there where——

Senator HAWKINS. Regarding death?

Dr. CROUT [continuing]. Where the people who got the replies are not very happy with them. Excuse me?

Senator HAWKINS. Regarding death?

Dr. CROUT. You mean do we get lots of letters on methyl-NC——

Senator HAWKINS. No; regarding a death in their family and regarding drugs given them.

Dr. CROUT. We get lots of letters from people about the drugs they are on. Sometimes they describe a drug I am on, would you send information about it, you know. They may describe a drug somebody in their family is on. So, this kind of letter is a relatively common kind of inquiry. The problem here is that for this drug, because it was an investigational drug, the staff does not have the usual information to send out with respect to marketed drugs. Ideally, we would have recognized that and created—spent some time with it and created a more personal reply. That did not happen. I regret that, and letters will be sent over my signature.

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[7] See p. 38.

Senator **Hawkins**. Where should people go for information about drugs?

Dr. **Crout**. To us. A perfectly good place to go. That is one of our jobs. We send out an enormous amount of information on drugs. The staff that does this has a very good record and gets a lot of compliments and has an extraordinary workload.

Senator **Hawkins**. I know that we get a lot of letters at our office, too. Since the Post series, we have been getting a lot more letters about the medicines and drugs that people are taking, and can we answer that. We have been referring them to you. I am most hopeful that you will have a more personal response to those that have taken the time and the trouble to write letters. I imagine, had this been addressed to you, Dr. Crout, rather than the Food and Drug Administration, that they would have gotten a more personal response. In the absence of not knowing your name and going to you directly, have you set up some kind of a system? Because of the heightened interest of all people in the United States who are paying attention to the Post series and suddenly wanting to know what drugs their parents or their children are on, have you a new system in place where they get a more personal response?

Dr. **Crout**. Well, to the extent we can. We have certainly got a system, a system—the mail does—this went to the right place and was handled from a system standpoint correctly. All I can say is the letter itself did not meet the mark. I apologize for that and will try to see that the ones coming in from your committee certainly do.

Senator **Hawkins**. Before I dismiss this panel, Dr. Crout, I would like to make a statement that we did subpena the witnesses that came before this subcommittee on Tuesday. I have read all my life about whistleblowers in Washington, D.C., and what happens to them if they are brave enough to tell the truth when they either want to tip someone off or whether they are brave enough to come if subpenaed, as this subcommittee did subpena those people.

I think your calling Dr. Wood and talking to her has a chilling effect on this investigation. I think this subcommittee has caused many thing to be done, which has been evidenced by Dr. DeVita and Dr. Brandt's comments on positive steps that have been taken this year, 1981. Since this subcommittee started looking into the management of NCI, there have been several new policies and procedures that have been put into place that are long past due.

This subcommittee, you know, is not made up of scientists, or doctors, or administrators. We are just using commonsense and logic. I certainly, as the chairman of this subcommittee, do not appreciate having one of our witnesses called before her boss. Whether you felt you intimidated her or not is really immaterial. She did feel intimidated and, as I stated before, called us last night at 10 p.m. and was very upset about the lasting feelings that she has now as an employee over there. And she was coming before this subcommittee to help all people in this entire land.

Dr. **Crout**. May I comment?

Senator **Hawkins**. Yes.

Dr. CROUT. I have faced that accusation before, which is always uncomfortable. But I must tell you I try to maintain communications and good communications with our staff. I talked with Dr. Hensley also. I have talked with Dr. Richman. And some of those people have come to me before hearings. To have communications go on back and forth I think is something that is absolutely essential in an institution.

I do not believe that you want to give the impression that management is not entitled to or should not deal effectively with its employees. In this instance you must understand that Dr. Wood, wittingly or not, gave an impression which she confirmed to me yesterday of intimidation or of pressure with respect to the integrity and the science of her reviews. And I have to contest that. I had to understand it first. And I now must contest it. She is under pressure to get her work done. And, if a boss cannot talk with employees on that issue, then there is no way to run the store.

I am sorry she called you, but I cannot agree that it is I that needs a lecture on the point. I am very sensitive to the point. And I agree with you wholeheartedly on the principle, but in this instance I cannot confirm to you from my perspective the impression that I believe she may have created with the committee. We simply differ in our points of view. I think I am entitled to state my point of view as she is entitled to state hers.

Senator HAWKINS. Well, we will pursue that with all of the witnesses that come before us because we intend to continue this investigation and also continue our oversight responsibilities of the management of the agencies that come before us.

I think we have heard that Federal regulations have been violated. We have heard that ordinary prudent management procedures have been violated; in effect, the reporting procedures have been violated. More importantly, I think the rights of cancer patients to full disclosure have been violated. So, as you go back and review the procedures and the practices that you have had in the past, hopefully, those new ones that you now have in place will be for the benefit of all of us.

We thank you for coming today.

Our next panel of witnesses are Mr. Alexander Morgan Capron and Ms. Barbara Mishkin of the President's Commission for the Study of Ethical Problems in Medicine and Behavioral Research. Mr. Capron is Executive Director and Mrs. Mishkin is Deputy Director of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. We are pleased you could be here today and share your expertise with the panel.

I understand you are going to summarize the statement that I have.

Mr. CAPRON. That is correct.

STATEMENT OF ALEXANDER MORGAN CAPRON, EXECUTIVE DIRECTOR, PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH, ACCOMPANIED BY BARBARA MISHKIN, DEPUTY DIRECTOR

Mr. CAPRON. Good morning, Madam Chairman. I am Alex Capron, as you said the Executive Director of the Commission. On my right is Barbara Mishkin, the Commission's Deputy Director.

With your permission, I will submit the full statement for the record and simply highlight central points for you now.

Senator HAWKINS. Fine.

Mr. CAPRON. Although I have some fairly critical things to say about the procedures by which regulations to protect human subjects are applied in research on cancer chemotherapy, I wish to make very clear at the outset that the President's Commission and its members have a personal interest in research on cancer therapies and have no desire to impede such research unduly or to spread alarm among the participants of such research. Several of the Commissioners have participated in cancer research as scientists or as subjects, including our chairman, Morris B. Abram, who has written candidly of his experiences since 1973 in experimental therapy for acute myelocytic leukemia, a normally fatal type of cancer of the bone marrow.

I need hardly tell this committee about the mandate of the President's Commission since the Commission was first conceived and authorized in 1978 by the Senate Committee on Labor and Human Resources. Since beginning its work in January 1980, the Commission has devoted a good portion of its effort to its charge of overseeing the adequacy of the rules and policies of all Federal agencies regarding the protection of human subjects of research and, in particular, the adequacy of the implementation of those rules. We are also preparing a report on our separate mandate to study the requirements for informed consent in research as well as therapy.

The Commission is studying several widely reported cases of misconduct in federally funded research as a window through which to view the current procedures for implementing Federal rules governing research with human subjects. One of those is a research project conducted at M. D. Anderson Hospital and Tumor Institute in Houston on an experimental anticancer drug, 5-methyltetrahydrohomofolate, referred to as MTHHF, which was administered to cancer patients without having been cleared by either the Food and Drug Administration or NCI for use in human subjects.

Looking at the protection of human subjects through that window, as illuminated by the report of a National Cancer Institute site visit team earlier this year, one comes away with many questions about the adequacy of NIH's implementation of its regulations on research with human beings. Among the areas of concern are:

First, plain failures of local institutions to comply with rules about the informed consent process that is intended to protect subjects' rights.

Second, apparent overemphasis by NIH on a paper reality that leaves it ignorant of whether its system of delegated review by

Institutional Review Boards, called IRB's, is actually protecting subjects in Government-funded research.

Third, an absence of any standards of what makes an IRB good or bad and inadequate communication by HHS of its expectations and how they can be fulfilled.

I will be happy to elaborate on each of these points in response to questions. Before explaining what the Commission is doing to correct these deficiencies, perhaps I should provide a few particulars on these points as illustrated by what has been learned about NCI-sponsored drug trials at M. D. Anderson Hospital.

First, in August 1978 the IRB at M. D. Anderson approved a protocol labeled DT78-31 for a phase I drug study on MTHHF. No direct therapeutic benefit to subjects was probable. Yet, the consent form approved by the IRB for that study gives the strong impression that the investigational drug is being given for therapeutic reasons. For example, after the space for the name of the drug appears the sentence: "I am about to receive a form of chemotherapy recommended by my physician. He has explained the potential benefits and hazards of this treatment to me."

Second, the consent forms fail to list the potential side effects or risks of the drug. Instead, the consent form misleadingly asserted that: "the amount of drug used solely for the pharmacology studies will be free of toxic effects."

Furthermore, this problem with the consent process was not limited to this single project. Last week, the hospital's vice president for research told two House subcommittees scrutinizing NCI that the consent form approved in this instance was the one generally used for phase I studies at the institution at that time. And a review of other studies conducted at M. D. Anderson compiled during a recent FDA inspection reveals boilerplate phrases in which subjects are asked to affirm having been told "a description of all known side-effects, discomforts and risks" and "alternative forms of therapy and alternative drugs and treatments," while no such statements were apparently received or approved by the IRB as required by HHS rules. Unfortunately, the FDA inspectors, like the NCI site team looking into the MTHHF case, seem either not to have perceived or at least not found worthy of comment problems such as these with the IRB's processes and consent forms.

HHS has delegated to the institutions that receive its research funds the responsibility to safeguard the rights and welfare of human subjects. Since it would be very burdensome for HHS to monitor the IRB's review of each research project, the department instead permits each institution to provide a written general assurance that the IRB will follow HHS rules. Unfortunately, nearly all of the effort of HHS officials has gone into accrediting institutions based on their formal submissions, and little attention has been paid to seeing whether the IRB's are meeting the expectations of HHS.

The NIH asserts that protection of subjects is assured through the multiple layers of review: From the local IRB, through the so-called study sections, to the councils of each institute. Problems may—and do—get identified at any stage. Yet, as the M. D. Anderson case illustrates, major problems may go unnoticed, in large part because the responsibility as well as the expertise of the peer groups at NCI is focused on the science, not the ethics, of protocols.

What reassurance can the Department provide that similar problems are not occurring elsewhere across the country today, or even at M. D. Anderson Hospital itself, in biomedical and behavioral research supported by Federal funds? If such reassurance is voiced by HHS, with what credence should it be received?

Regrettably, as far as the President's Commission has been able to learn, problems of the sort illustrated here arise because the Department has not adequately communicated its expectations to those conducting human research under its auspices; it can provide no assurance of compliance with its policies and procedures because it does not know how well IRB's are functioning. In the 3 years since the National Commission made its recommendations on IRB's, nothing has been done to implement the important compliance function of HHS which to the National Commission was as important as HHS's accreditation function. Although NIH has asserted that this function is being undertaken, it has not in fact instituted site visits, IRB audits, or the like. NIH's top official for extramural research, William Raub, has recently announced that site visits will be used to spot check animal labs conducting federally funded research to assure that the labs are obeying Federal rules. Should not human beings be given equal protection?

Although policies on the protection of human subjects in federally funded research were first announced in 1966, there are still today no benchmarks established by HHS for what would constitute adequate performance by an IRB. Is it acceptable, for example, for the continuing review of each protocol by the IRB required on at least an annual basis to occur in such a way that the IRB does not obtain the actual consent forms and actual data for each protocol?

Not just standards for judging IRB's but substantive rules to aid their decisionmaking are also wanting. Difficult issues in research with human beings do not go away simply by being delegated to local IRB's. "Out of sight, out of mind" ought not to be the motto of those entrusted with the high responsibility of protecting subjects in research supported by Federal funds.

For example, neither FDA nor NIH has provided guidance to IRB's on how to judge whether a phase I study of a cancer drug may be termed "therapeutic" when its purpose is to study clinical pharmacology and toxicity. To do so would seem to contradict general FDA policy; yet everyone knows that cancer researchers do exactly this, and vehemently defend this position, apparently without correction or further advice from FDA and NIH. Nor have the Federal officials established guidelines that would lead institutions to separate the role of clinical investigator from that of physician. The merger of researcher with healer not only compromises the subject's ability to give—or withhold—consent in a free and informed fashion but also deprives the subject of an independent advocate and protector during the course of the experiment.

STEPS BEING TAKEN TO IMPROVE THE SITUATION

Institutions clearly need a helping hand as well as a watchful eye if they are to achieve the protection of human subjects promised in the HHS regulations. The problems we have described are not limited to experiments sponsored by NCI but extend to all human research funded by NIH.

The President's Commission is developing a guidebook as an educational and procedural tool for IRB's. The Commission has also begun testing out in about a dozen settings procedures that could be used on a periodic or spotcheck basis for site visits to institutions by peers knowledgeable about IRB's. This type of compliance activity will need to be compared with audits or IRB records such as those carried out by FDA inspectors for drug trials sponsored by pharmaceutical companies and with self-monitoring IRB's. For all of these, one must see whether standards for assessment beyond formal compliance can be developed. And the ability of each method to educate IRB members about their responsibilities and to encourage institutional respect for IRB's must also be assessed.

Rather than simply reiterate previous recommendations, the President's Commission is actually developing and testing out the necessary materials and procedures in order to demonstrate how such steps can be made feasible. By the time we complete our work a year from now, I hope to be able to report not only the successful demonstration of the necessary materials and procedures but also that the relevant officials at NIH are prepared to implement these steps.

Without adequate procedures for monitoring compliance with its rules, HHS cannot assure the public that human subjects are being protected. Without that assurance, public confidence in and support of research will be greatly diminished. These concerns are particularly important in the case of cancer research whose subjects are both at such great risk and in such great need of therapeutic breakthroughs.

Thank you, Madam Chairman.

[The prepared statement of Mr. Capron follows:]

STATEMENT OF ALEXANDER MORGAN CAPRON

Good morning, Chairman Hawkins and members of the committee. I am Alexander Capron, Executive Director of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. I am accompanied today by Barbara Mishkin, the Commission's Deputy Director.

During the course of this testimony, I will have some fairly critical things to say about the enforcement of regulations to protect human subjects in research on cancer chemotherapy. Therefore, I want to make very clear at the outset that the President's Commission and its members have a personal interest in research on cancer therapies and have no desire to participate in any movement to impede such research unduly or to spread alarm among the participants in such research. Our chairman, Morris B. Abram, has written candidly of his experiences as a subject since 1973 of experimental therapy for acute myelocytic leukemia, a normally fatal type of cancer of the bone marrow. Another commissioner underwent surgery, radiation and chemotherapy for cancer within the past year. Still another member of the Commission is engaged in basic research at the Memorial Sloan-Kettering Cancer Center, specializing in research on interferon. Finally, all the Commissioners recognize the importance of clinical research, an activity in which many of them have been engaged for many years.

As important as progress through clinical research may be, it cannot be sought at the price of patients' dignity and well being. Assuring the proper conduct of research is an important responsibility of research sponsors, particularly when the sponsor is the Federal Government. Besides being an ethical imperative, it is also--as the outcry over press reports about drug trials sponsored by the National Cancer Institute demonstrates--a necessary condition for maintaining public confidence in the research enterprise.

ROLE OF COMMISSION

The President's Commission is charged by Congress under P.L. 95-622 with overseeing the adequacy of the rules and policies of all federal agencies regarding the protection of human subjects of research as well as the adequacy of the implementation of those rules. We are also specifically asked to study informed consent for research. In the course of our work we have uncovered serious weaknesses in the enforcement of the research regulations of the Department of Health and Human Services (HHS). Sadly, these deficiencies are illustrated with particular force by a recent site visit, which we shall discuss today, convened to investigate a research project funded by the National Cancer Institute (NCI). Because our mandate is to review federal rules and the adequacy of their implementation rather than to adjudicate individual cases, my remarks will focus primarily on deficiencies in HHS procedures (as revealed in the site visit report) and on steps now being studied by the Commission to remedy these deficiencies.

AN ILLUSTRATION OF FAILURE IN THE REVIEW PROCESS

The Commission has been studying several widely-reported cases of misconduct in Federally-funded research as a "window" through which to view the current procedures for implementing Federal rules governing research with human subjects. A case we reviewed recently involved a research project at M.D. Anderson Hospital and Tumor Institute, a part of the University of Texas System Cancer Center in Houston.

Throughout my testimony I shall refer to the attached report of a National Institutes of Health (NIH) team that conducted a site visit to the Hospital in July 1981 to investigate the project and the hospital's research review procedures. NIH does not routinely make site visits to examine the conduct of the research it sponsors or the procedures actually employed to protect human subjects. This site visit was triggered by concern that a serious breach of several provisions of federal regulations had been violated.

An NCI employee happened to see a brief medical journal report by M.D. Anderson investigators of the use on six cancer patients of a new drug, 5-methyltetrahydrohomofolate (referred to as MTHHF), which had not been cleared by either the Food and Drug Administration (FDA) or NCI for use in human subjects. Subsequent investigation at NCI revealed that the compound had been provided to the principal investigator under a contract specifically limiting use of the drug to animal research. The NCI wrote to officials at M.D. Anderson, suspending any further work by the principal investigator and announcing a site visit to take place on July 13, 1981.

What is of concern to the Commission are certain questions about the consent procedures and the institutional review procedures at M.D. Anderson as revealed in documents examined by the site visitors and included in the report to the Acting Director of NIH. A total of nine people traveled to Texas for that site visit. Their charge was to answer the following questions:

a. Was harm done to any patient? And if so, to what extent?

b. Why was [the drug] administered to humans without an FDA approved IND application?

c. Was informed consent obtained?

d. Had the protocol used been approved by the appropriate institutional committees?

e. Were [the investigator's] administrative supervisors aware of the conduct of the study in question?

f. Had any similar violations occurred?

g. Are the current institutional procedures for investigational drug studies adequate?

h. What steps had the institution taken in response to the incident to see that it did not occur again?

HHS RULES AND POLICIES ON HUMAN RESEARCH

The HHS system for protecting human research subjects depends for its implementation on Institutional Review Boards (IRBs) at the local level. In order to receive funds to conduct research with human beings from the Department of Health and Human Services (or, incidentally, from a number of other Federal agencies), an institution must provide a written assurance, satisfactory to the Department, that it has an IRB in place and that the institution, through the IRB, will comply with the Department's regulations for the protection of human subjects.

In January 1981, the Department recodified its regulations on human research in light of recommendations made by the National Commission for the Protection of Human Subjects between 1974 and 1978. The parts of the regulations that are germane here are substantially the same as the preexisting regulations which were promulgated in 1974 and which were in force at the time the research in question was conducted at M.D. Anderson. (In what follows, I shall employ the numbering of the 1974 regulations for simplicity's sake; like the 1981 regulations, these are codified in Title 45 of the _Code of Federal Regulations_.)

Section 46.110 of the 1974 regulations required documentation of the "actual procedure utilized in obtaining legally effective informed consent and the basis for Institutional Review Board determinations that the procedures are adequate and appropriate." The documentation of consent was permitted to take one of two forms in biomedical research. Typically, a subject is provided with "a written consent document embodying all of the basic elements of informed consent. This may be read to the subject or to his legally authorized representative, but in any event he or his legally authorized representative must be given adequate opportunity to read it." The regulation required that the document be signed by the subject or his legally authorized representative, and that "Sample copies of the consent form as approved by the Board ... be retained in its records."

Alternatively, a "short form" written consent document was permitted, which would indicate "that the basic elements of informed consent have been presented orally to the subject or his legally authorized representative. Written summaries of what is to be said to the patient are to be approved by the Board." The rules required that the form be signed not only by the subject or his legally authorized representative but also "by an auditor witness to the oral presentation and to the subject's signature. A copy of the approved summary, annotated to show any additions, is to be signed by the persons officially obtaining the consent and by the auditor witness." Again, sample copies of the consent form and of the summaries as approved by the Board must be retained in its records.

According to 45 C.F.R. §46.103(c), the information to be disclosed to prospective subjects had to include:

> (1) A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;
> (2) A description of any attendant discomforts and risks reasonably to be expected;
> (3) A description of any benefits reasonably to be expected;
> (4) A disclosure of any appropriate alternative procedures that might be advantageous for the subject;
> (5) An offer to answer any inquiries concerning the procedures;
> (6) An instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject; and

> (7) With respect to biomedical or behavioral research which may result in physical injury, an explanation as to whether compensation and medical treatment is available if physical injury occurs and, if so, what it consists of or where further information may be obtained. This subparagraph will apply to research conducted abroad in collaboration with foreign governments or international organizations absent the explicit nonconcurrence of those governments or organizations.

THE IMPLEMENTATION OF THE HHS RULES AT M.D. ANDERSON

The University of Texas System Cancer Center had an approved "general assurance" on file with the Office for Protection from Research Risks at NIH, under which its IRB--called the Surveillance Committee--was, among other duties, to review the risks and benefits of all research on human subjects and the informed consent materials for all such research.

In June 1978, Dr. Stephen Hall prepared a research protocol for Phase I study of MTHHF, which was submitted to the Surveillance Committee by Dr. Gerald P. Bodey, Chief of Chemotherapy and Infectious Diseases. The protocol (at pages 41-58 of the site visit report) describes the objectives of this test on human subjects as:

(1) To determine the maximum tolerated dose of MTHHF administered by single dose intermittent, intravenous infusion;

(2) To determine the qualitative and quantitative toxicity and reversibility of toxicity of MTHHF administered in this fashion; and

(3) To investigate the clinical pharmacology of MTHHF and rationale for dose and schedule chosen.

In short, no direct therapeutic benefit to subjects was anticipated, and this study fit the FDA description of a "Phase I Study":

> Phase I starts when the new drug is first introduced into man--only animal and in vitro data are available--with the purpose of determining human toxicity,

> metabolism, absorbtion, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; Phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. (21 CFR §312.1(a), see para. 10(a) of Form FS-1571 described therein.)

A basic confusion in cancer research--a point that the NCI, NIH and FDA have never resolved--is whether a Phase I cancer study, designed to test a drug's pharmacokinetics and toxicity, can be described as "therapeutic research." In non-cancer studies, Phase I drug tests are usually conducted with normal volunteers, so that the subjects' medical condition will not interfere with the measurements of the drug's activity in the human body. Obviously, in such cases, there is no suggestion that the subjects should expect any benefit from the participation in the research. With cancer drugs, however, toxicity is such that even Phase I tests are conducted on cancer patients, often when no other treatment seems to offer hope of recovery.

Neither FDA nor NIH has provided any guidance to IRBs on how to judge whether a Phase I study of a cancer drug can be termed "therapeutic." Thus, IRBs are left to their own devices to make this determination, so necessary for evaluating the fairness of any reference in the consent documents to "therapy." The difficulty of making the judgment is starkly displayed in the "check lists" filled out by two members of the IRB at M.D. Anderson for the 1978 protocol on MTHHF. Dr. Alexander Wang replied "yes" to "The protocol is therapeutic in intent," while Dr. W. W. Sutow checked "no." Despite this inconsistency, the protocol, which was assigned number DT78-31, and the accompanying consent form were approved by the Surveillance Committee (IRB) on August 23, 1978. (Memoranda and "review check lists" from two IRB members are in the record, at pages 59-62.)

Whether the label "therapeutic" or "nontherapeutic" is attached to a research procedure, it is in any case the responsibility of the IRB to assess, for each protocol, the likelihood of direct benefit to subjects from participation in the study and to assure that prospective subjects will be fairly--and clearly--informed of the correct assessment of that likelihood (or unlikelihood).

The bottom line is that the official NCI site visit record contains no discussion or documentation of how the IRB resolved this question. Since the consent form itself is no model of clarity or candor, the clear impression is left that either the site visitors or the IRB, or both, failed to recognize the significance of these factors.

THE SPECIAL PROBLEMS WITH "INFORMED CONSENT"

The approved consent form is described in the documents (and subsequently in Congressional testimony) as the standard one in use at M.D. Anderson for Phase I antitumor therapy. This form gives the strong impression that the drug undergoing Phase I tests is being given for therapeutic reasons. For example, after the space for the name of the drug, appears the sentence: "I am about to receive a form of chemotherapy recommended by my physician. He has explained the potential benefits and hazards of this treatment to me" (p. 57). In fact, as one reviewer noted, the consent forms actually failed to list the potential side effects of the drug though promising a "detailed explanation of the therapy procedures and the purpose of this therapy" (emphasis added).

No statement of what (if anything) additional would be told to subjects about the potential for harm was provided to the IRB in 1978 when it approved the study, even though one reviewer drew special attention to the risks. Side effects reported from studies in dogs and monkeys were described in the protocol as: "loss of appetite, thirst, emesis, diarrhea, rectal bleeding, salivation, dehydration, weight loss, tonic-clonic convulsion ,incontinence (urine and stool), lethargy, and licking of the lips" (p. 43). Moreover, the major objective of this Phase I study was to determine the maximum tolerated dose--that is, the highest dose that a human subject can bear before the following toxicities occur: "severe meolytic anemia,...congestive heart failure, life-threatening arrythmias,...severe diarrhea requiring hospitalization for fluid replacement,... coma, seizures, nerve paralysis, progressive mental deterioration or weakness" (p. 54).

Although the project approved by the IRB was intended to ascertain the toxic effects of various MTHHF dosages, the consent form asserts that "the amount of drug used solely for the pharmacology studies... will be free of toxic effects." In testimony before Congress last week, oncologists stated that no therapeutic effect from a cancer drug would ever be anticipated unless the dose is large enough to be possibly toxic. Thus, a consent form that promises both therapeutic effect and lack of toxic side effects seems by definition to fail to give subjects a fair representation of the matter. Yet the IRB at M.D. Anderson, approved a consent form containing these contradictory statements.

Although approved, protocol DT78-31 was not carried out at that time. Yet two years later, another investigator at M.D. Anderson used MTHHT in a lower dosage and with different standards for subject selection without further approval by the IRB and without an IND for the drug. Furthermore, the site visit records also do not show that the subjects in the experiment actaully carried out in 1980 were warned of the spinal taps to be performed, nor is there any record that they were told whether spinal taps were solely for research purposes or necessary to safeguard their health once they had taken the experimental drug.

Finally, examination of other consent forms approved by the Surveillance Committee at M.D. Anderson reveals serious deficiencies in institutional procedures, which suggests that the MTHHF case was not an isolated event.

THE COMMISSION'S CONCERNS AND PROJECTS

How can the lofty promises of protection provided by the HHS regulations have fallen so short at the M.D. Anderson Hospital without anyone at NIH or FDA being aware of the deficiences? The short answer is that, despite its representations to the contrary, NIH has failed to take steps to assure institutional "compliance" with its rules (in the words of the National Commission). This problem is not limited to the NCI but exists in all research funded by the Department.

The consequences of the deficiences in NIH's communication with, and knowledge about, what is actually going on was manifested in the MTHHF experiment at M.D. Anderson. Just last week, the Vice President for Research at M.D. Anderson told two House subcommittees scrutinizing the NCI that the consent form approved in this instance was the one generally used at that institution in 1978. And NCI officials have stated that review groups at the Cancer Institute look at all the protocols and the consent forms approved by the IRBs. Yet, as already described, that form plainly failed to comply with applicable regulations in effect since 1974 as well as identical policy provisions that have governed research supported by HEW grants and contracts since 1971. (The Institutional Guide to DHEW Policy on Protection of Human Subjects, U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, December 1, 1971, at 7-8, 15.)

How could such clear violations have gone undiscovered--and uncorrected--by NIH for seven years? Indeed, what reassurance can the Department provide that similar problems are not occurring elsewhere across the country today--or even at M.D. Anderson Hospital itself--in biomedical and behavioral research supported by federal funds? If such reassurance is voiced by HHS, with what credence should it be received? Are the review groups at NCI properly trained for this aspect of their review?

Regrettably, as far as the President's Commission has been able to learn, problems of the sort illustrated here arise because the Department has not adequately communicated its expectations to those conducting human research under its auspices; it can provide no assurance of compliance with its policies and procedures because it does not know how well IRBs are functioning. Indeed, although policies on the protection of human subjects in Federally-funded research were first announced in 1966, there are still today no benchmarks established by HHS for what would constitute adequate performance by an IRB. Is it acceptable, for example, for the "continuing review" of each protocol by the IRB required "on at least an annual basis" to occur in such a way that the IRB does not obtain the actual consent forms and actual data for each protocol?

Institutions clearly need a helping hand, as well as a watchful eye, from HHS if they are to achieve the protection of human subjects promised to the American people in the HHS regulations. The President's Commission is developing a "Guidebook" as an educational and procedural tool for IRBs; the Commission is also testing out procedures that could be used, on a periodic or "spotcheck" basis, for site visiting IRBs.

There is nothing extraordinary about these developments. NIH's top official for entramural research, William Raub, has recently announced that site visits will be used to "spot check" animal labs conducting federally funded research to assure that the labs are obeying federal rules. Shouldn't human beings get equal protection? The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research thought so. In 1978 it recommended that:

> Site visits, audits of IRB records, and other compliance activities should be conducted routinely to assure continuing quality control of the performance of IRBs. The compliance effort should be aimed at educating, improving performance of IRBs, and providing needed advice. Where necessary, however, failure by investigators, institutions or IRBs to meet their responsibilities should be subject to sanctions ranging from warnings to loss of IRB accreditation and consequent ineligibility to receive federal funds for research involving human subjects or refusal by a regulatory agency to accept data. (National Commission, Report and Recommendations: Institutional Review Boards 11-12 (DHEW Pub. No. (OS) 78-0008).)

The problem is simply that in the three years since the National Commission made that recommendation, nothing has been done to implement this important "compliance" function of HHS, as the National Commission termed it. Although NIH has asserted that this function is being undertaken (see 44 Federal Register 47690, August 14, 1979), it has not in fact instituted site visits, IRB audits or the like; and while the FDA currently "inspects" IRBs (by examining the paper record of a single drug through steps of the IRB's approval process), its practices also leave a good deal to be desired.

Rather than simply reiterate these recommendations in the face of Departmental inaction, the President's Commission decided to attempt to develop the necessary materials and procedures, in order to determine how such steps could be made feasible. A year from now, when the Commission is completing its Second Biennial Report on the Protection of Human Subjects, I hope to be able to report to you not only that successful materials and procedures have been developed, tried out in 10 to 12 institutions, and refined, but also that the people with whom we are coordinating our efforts in the Office for Protection from Research Risks and in the FDA are prepared to implement these steps.

Without adequate procedures for monitoring compliance with its rules, HHS cannot assure the public that human subjects are being protected. Without that assurance, public confidence in--and support of--research will be greatly diminished. Thus, we hope that our remarks about the need for improvements in procedures for protecting human subjects will be taken in the spirit in which they are intended: to protect a very important research enterprise from loss of public confidence and support--without which the research itself would be impossible. These concerns are particularly important in the case of cancer research whose subjects are both at such great risk and in such great need of therapeutic breakthroughs.

(Note: In the interest of economy, the reports and other material referred to in Mr. Capron's statement were retained in the files of the committee (due to its voluminous content) where it will be available for research upon request.)

Senator HAWKINS. Mr. Capron, an investigation of the M. D. Anderson Cancer Center was undertaken when it was learned that cancer patients were being administered MTHHF which had been provided to a principal investigator for use in drug animal research only. You, too, have been studying the report of this investigation, have not you?

Mr. CAPRON. Yes.

Senator HAWKINS. What did the Commission find was wrong with the informed consent procedures?

Mr. CAPRON. The consent form, which is the only aspect that is revealed about the informed consent procedure in the documents collected by the NCI site visit team, does not give the impression that the subject is being asked to undergo a phase I study. The impression is given that the subject is undertaking a beneficial therapy.

Senator HAWKINS. Did the institutional review board function properly at M. D. Anderson?

Mr. CAPRON. To the extent that it approved that statement, to the extent that it did not require the revelation of side effects and toxicities which included coma, seizures, progressive paralysis, and the like—these are all the various risks that the toxicity study was designed initially to discover—it did not function well. Some of those points were identified by individual members of the IRB, but the IRB apparently did not have the information at hand or did not insist that it be revealed to the subjects.

Senator **Hawkins**. Ms. Mishkin, your principal function has been to review Federal regulations designed to protect human subjects. Much of this activity has focused on HHS. Are you satisfied that the Department has provided you with ample opportunity to make a fully effective review?

Ms. **Mishkin**. We have had a long series of correspondence with the Secretary of HHS and various others in the Department with respect to their policies and procedures for investigating reports of misconduct at various institutions and for responding to them at the Federal level. We are not satisfied yet that we understand what their policies and procedures are. Our chairman wrote to Secretary Harris in September 1980 putting a number of questions to her about HHS policies and procedures. She wrote back 2 months later that Dr. Frederickson, who was then Director of the NIH, was studying the problem, and she would get back to us after she had a report from him.

In April of this year, Secretary Schweiker answered our letter, having then taken over as Secretary of that Department, and many of his answers were essentially: "It depends on the facts of a particular case." We asked, for example, how they decide what material failure to comply with regulations would be and how they decide when to tell review committees that a scientist is under serious investigation for noncompliance, so that those review committees would not automatically provide additional funds to that scientist. And in many of the answers the Secretary gave, it was essentially: "It depends on the facts of a particular case."

At a subsequent Commission meeting, the Commissioners requested that a letter go from our chairman, Mr. Abram, to Secretary Schweiker, asking for a meeting with him, so that staff of the Commission could explain to him more fully what our concerns were, and emphasizing that we were not asking about details of ongoing investigations. We know that those will be forthcoming when the investigations are complete. We are asking for standards for initiating investigations and standards for proceeding with those investigations and taking Federal action when the investigations are complete.

In August, Secretary Schweiker wrote to the chairman that: "It is not appropriate for me to meet with you at this time," and that is the last that we have heard from the Department on that subject until just last week.

Last week Secretary Schweiker wrote a letter to Mr. Abram, dated October 28, that he is now prepared to meet with him to discuss the Department's policies and procedures for dealing with reports of research fraud and abuse.

Senator **Hawkins**. Do you have an appointment for that meeting?

Ms. **Mishkin**. We are in the process of trying to set that up. Our chairman has been overseas for the last several weeks. We are trying to set something up at his convenience and the convenience of the Secretary.

Mr. CAPRON. Madam Chairman, if I might add. The letter from Secretary Schweiker of April 15 came 2 weeks after we testified before a House committee investigating the National Cancer Institute trials last spring. The letter from Secretary Schweiker this week came a day after other testimony. It is part of the appreciation we owe to the committees on the Hill, but occasionally requests of ours which get overlooked seem to get attention once the committees show interest in the same subject.

Senator HAWKINS. Mr. Capron, you have spoken of the three legs of responsibility in assuring patient safety in phase I trials. You describe the Institutional Review Boards as the fulcrum of that responsibility. Are you satisfied that the approximately 1,000 IRB's are performing effective oversight functions?

Mr. CAPRON. Well, I do not want to take exception with your number, but I believe there are about 550 general assurances. They may amount to a larger number of IRB's. There are also a number of institutions, I believe several thousands, that have special assurances. So, we are actually talking about an even larger number than you mention.

It is an article of faith now in the research community that those Institutional Review Boards are doing a good job. I think there is no way for me to give you an answer to that based upon extensive data. We thought one of our responsibilities was to get the answer to that question from the Department. When we turned to the Department, we found that they do not have the information to provide that because they have not engaged in compliance activities that were recommended by the National Commission.

When one does look carefully at the cases, one sees serious problems. I think the basic point of our testimony today is not to criticize any particular research institution. When I used an example, it was simply because that happens to be a case where something so flagrant occurred that it prompted a highly unusual investigation. But, if one receives the assurances, as you heard this morning from Secretary Brandt and Dr. DeVita and so forth, that everything is working well, and then one looks at a single case at what is regarded as a highly respected institution—and we have looked not only at that institution but other well-known medical facilities—and sees immediately serious problems, one says that one cannot take those reassurances with quite as much credence as we were being asked to take them.

Senator HAWKINS. In your testimony you make frequent mention of the need for site visits. What would you hope these site visits would accomplish?

Mr. CAPRON. We see the site visits as accomplishing a good deal more than the present FDA inspections. Indeed, right now we believe that there seems to be a lack of communication or has been a lack of communication between the Cancer Institute, the rest of the NIH (with which the Cancer Institute also seems to have a special relationship besides its special relationship with the FDA) and the FDA. And it may well be that the FDA monitors do not fully understand, particularly when they are looking at research which is not only drug research but federally funded drug research, that certain rules about informed consent have to be complied with.

As I mentioned, that does not seem to have turned up in the FDA inspections. So, we hope that these site visits would do more in terms of bringing people to the institutions who are familiar with IRB functioning in a way which the FDA inspectors are.

We also believe that they should serve an educational function. They are not solely or maybe even primarily policing efforts, but they could be, we believe, an outreach from the NIH, bringing in people who are experienced with IRB functions to discover failures and misunderstandings that keep an IRB from doing its job and protecting human subjects.

We have begun our process of studying this process. We have had several site visits. We have about 10 more scheduled in the next few months.

I would not want to report on the first ones other than very briefly to say that both the institutions that were visited by our team stated to us that they appreciated the visit, they learned something from it. And the members of our staff who are conducting that process feel that we will some months from now be able to report on a method that will be successful.

I do not mean to exclude by that other means of encouraging IRB's to do their job from education to the auditing of their records. These were all things which were recommended by the National Commission. The Department stated in 1979 that it was already in compliance with that recommendation. As far as we can see, they are not and today they admit that they do not do those site visits. There is a disagreement, an incongruence between their statement in 1979 and what it turns out they do once they are cross-examined on it.

Senator HAWKINS. Ms. Mishkin, have you read the report submitted to the National Cancer Institute entitled the 'Effect of Regulations on the Conduct of Cancer Treatment Research?"

Ms. MISHKIN. Yes, I have read at least one volume of that report.

Senator HAWKINS. One volume? How did you obtain a copy of that report?

Ms. MISHKIN. It was provided to me by a member of your staff, Madam Chairman. I was unable to get it from the Cancer Institute.

Senator HAWKINS. Why not?

Ms. MISHKIN. I was told that it had not yet been reviewed by the Institute and therefore was not releaseable.

Senator HAWKINS. Are you familiar with the report's primary recommendation that there be three categories of research with different levels of regulatory control?

Ms. MISHKIN. Yes, I am.

Senator HAWKINS. How do you feel about that recommendation?

Ms. MISHKIN. I can tell you how I personally feel. The Commission has not reviewed that or commented on it. I would be very troubled about implementing the suggestion that cancer research of any sort be subject to less stringent review than it now currently undergoes. The problem is, first of all (as we have seen through these hearings and other hearings in the last week or so) there is not unanimity of understanding as to whether a phase I drug test in cancer chemotherapy has any reasonable probability of benefit to the patients who participate in that research.

The therapeutic intent down the line to subsequent cancer patients is not sufficient to carry with it a therapeutic probability, necessarily, for the patients who are asked to participate in those studies. Therefore, especially because cancer patients are particularly vulnerable, we need to be sure that the information provided to them about the possible risks and the likelihood of benefit, if any, from that particular research protocol is a fair presentation. And the only way to do that is to have people other than the cancer researchers review the consent documents, along with the protocol of what they propose to do, and make sure that the one is an adequate and fair representation of the other.

A second worry is that which we have mentioned earlier: The dual role of the physician and scientist in cancer research, which I can elaborate further if you wish.

Mr. CAPRON. Madam Chairman, if I may inject one note here, since you have raised this question of this study which was sponsored at the cost of about $300,000 by the National Cancer Institute to examine how regulations were making cancer research more difficult. Part of that report which was supplied to us states something which I believe is rather troubling. And that is that on page 4 of the task force sixth report, which I believe your staff has, there is a description of the "diversion," in the word of the authors, of the contract effort at the request of the National Cancer Institute to mobilize the interested cancer researchers to lobby against certain of these regulations.

In reading that, it was a matter of particular interest to the Commission because we are engaged in a study of the very difficult issue of whether compensation should be provided to subjects who are injured in research. Since we have begun that effort, we have been inundated with a stream of correspondence from cancer researchers around the country arguing against any such proposal, which was one of the very issues being discussed at the meeting which was held with National Cancer Institute funds, in which this effort to mobilize the community to lobby was raised.

It seems to us that it is quite proper—and we have indeed sought throughout our work the input of all the institutes and other Federal agencies—for them to make their views known directly to us. And it is equally proper for the interested community to do so. But, for the National Cancer Institute to, in effect, recruit a front organization to make it appear as though there is a national uprising on this subject when in fact it is something which the Cancer Institute is sponsoring strikes us as a rather odd way for a Federal agency to deal with other Federal bodies.

I know—and this may just be my personal prejudice—that I take differently a letter which we receive, apparently spontaneously, from someone who steps away from their lab or from taking care of patients to write us something that is close to their heart, something that is very important to them, than I would from an official document from the National Cancer Institute, which I expect to take a particular position. We take it into account, but it has a different impact.

That is one of the things which we did not know of prior to the existence of this report, which is absolutely bold face about the fact that a mobilization was being run through the diversion of funds that was given under this contract which was supposed to be a study grant.

Ms. MISHKIN. If I might——

Senator HAWKINS. We intend to get a response from the NCI on this matter. I would be happy to furnish it to you.

Mr. CAPRON. Thank you.

Ms. MISHKIN. I was just going to add that I find it puzzling if they were concerned about the recommendations being drafted or under preparation by the National Commission (the predecessor to this Commission), that they did not make it known to us. I went back and looked at the formal and informal communications and presentations that we had from various institutes at the NIH through the 4 years that the National Commission was in business, and we did have presentations from the National Institute of Child Health and from the National Institute of Mental Health and various other institutes and components of HHS. But I did not find any documentation in the records I still retain from that Commission of communications from the National Cancer Institute on any of the subjects which are under discussion in the report which I have read.

Senator HAWKINS. Mr. Capron, the NIH and FDA share responsibility for the conduct of institutional review boards. Are you satisfied that the flow of information between the two, NIH and FDA, allows for effective cooperative action?

Mr. CAPRON. We have had statements particularly from the NIH indicating their awareness of past inadequacies. As long ago as our second Commission meeting, we had testimony on that point both from the FDA and the NIH. We are continuing to work on that.

I cannot say that I am satisfied because these problems continue to arise. We are working with them. We plan to continue to do so. I hope that that communication will work. I think sometimes the Commission is a little bit like a dog barking at the heels of a large herd of cattle. The Federal bureaucracy moves very slowly, and we are an irritant. And it makes personal relations with some of the people we have to deal with, I am sure, more difficult for them than they would wish. Perhaps the congressional committees, as I suggested before, serve as the actual cowboys that get the whole thing going. We are a small dog.

But we see some progress and we do see greater cooperation, greater efforts to share information. Certainly, when we began our work, we quickly discovered that reports that were coming to the FDA were not necessarily getting to the NIH and vice versa. We hope that that will improve and particularly on the monitoring of IRB's. There is no indication in the file that the NCI site visit team that went to M. D. Anderson had the benefit of the FDA's prior review of that same Institute.

So, no, I do not think it is working yet, but we are hopeful that, with continuing efforts, we can get it to work.

Senator HAWKINS. Do you have a suggested list of guidelines for effective oversight of IRB's?

Mr. CAPRON. As I say, our major effort at the moment is trying to develop a system which we are already testing out, and not just making a recommendation but trying to sort of bring forward a body and say: See, this thing works; we have tried it out, and here is how it works, and here is how it would be able to merge the responsibility the FDA has with the NIH's.

Many of the NIH general assurance IRB's are the very ones that do also review drug research because they are the major research institutions. There are some that do not have general assurances and only do drugs, and there may be some that only have general assurances and do not do drugs. But there is a large area of overlap. And we think this system could work for both of them and could be a saving of resources, a more appropriate form of review than the FDA now gives, and certainly more appropriate than the absence of review that the NIH now gives.

Senator HAWKINS. Ms. Mishkin, can you give us any indication of the direction that those recommendations should take?

Ms. MISHKIN. Yes, our biennial report to the Congress, which is due in December of this year, will contain some recommendations for improving the system of both institutional and Federal response to reports of misconduct in federally funded biomedical research. Those recommendations are now in draft form and will be considered by the Commission next week at their meeting. They include suggestions for improving the knowledge of all who work on research teams about the existence and the functions of institutional review boards.

We have found in some of our testimony that, although principal investigators who have to submit paper to the IRB's know about them, it sometimes happens that nurses and other people dealing with the subjects do not know about IRB's. We want to assure that the grantee institutions have a system in place for an orderly, a fair, and a timely response to reports of any problems occurring in biomedical research with human subjects. And we want to make sure that the Department of Health and Human Services also has a clear and an unambiguous set of standards and policies for responding when they receive reports of misconduct. We would like to see that they have clear standards for deciding whether to go ahead and give an investigator further public moneys to do his research while he is already under investigation for misconduct in a research protocol for which he received a previous award.

We want to protect the rights of the people who are accused of misconduct. Not all accusations are well founded. Those accused must have a full and a fair hearing, and it must be a prompt hearing.

We also want to protect the whistleblowers, as they are called. So long as we lack a system of oversight, the Government depends on those whistleblowers for its information about misconduct. And it is not going to get information from people out in the real world unless those people are protected from retaliation at their own institutions.

Senator HAWKINS. Thank you. Mr. Capron, do you have any other suggestions to insure consistent and full degree of informed consent?

Mr. CAPRON. One of the suggestions which I mentioned and I believe Barbara Mishkin has also just mentioned is encouragement to all institutions that they make sure that subjects, particularly very sick subjects, have a person who is serving in the role as physician or healer separate from the person who is the physician investigator. And I do not think that this is a matter of pie in the sky. I am a fairly practical person, and I like to think about things that really can be done.

Last week the House committee was told by Dr. Ultman of Chicago that at his institution physicians in the cancer research program undergo a monthly rotation so that 1 month they are acting as a researcher, and the next month they step out of that role into the role of physician to be the patient's advocate and protector.

I think, if the Department were to invest the same kind of energy and attention in the protection of human subjects as it does in research on human subjects, if there were some of the support and recognition for people who excel on the human side of treatment, if there were greater dissemination of ideas like this, if there were more attention to the need for physicians to have training in communication and to have whatever support they need, then one might see some real changes. As Dr. Brandt testified, some of them are very uncomfortable with the role of giving information about suffering and dying, and as Dr. DeVita said, when you are talking about cancer, people have great difficulty in describing it to the patients and they are as fearful as the patients are. If a doctor is in that position, he ought not to be the one who is having to talk to the patient about participating in the research because he is not going to be willing to face up to the fact that sometimes what you are asking a sick person is: Will you do something for the benefit of science? And, unless that is made clear, that this is not being offered to you for your own benefit, but we are asking if you want to make a contribution to knowledge, and the person is comfortable in talking about great risks because of this imminence of death or the like, it is not going to work.

So, I am saying we ought to give as much attention and as much recognition for people who excel at that and disseminate their methods and give whatever support is necessary to people doing that. It is much easier to give attention to the breakthroughs in science. Those are crucially important, but they should not be bought at a price of the lack of communication and people brought into studies about which they are unaware.

Senator HAWKINS. We thank both of you for sharing your views with us today and look forward to working with you in the future as this subcommittee's work continues. Thank you.

Mr. CAPRON. Thank you, Madam Chairman.

Senator HAWKINS. Our next witness is Dr. Charles LeMaistre, president of the University of Texas System Cancer Center.

While Dr. LeMaistre is coming forward, we regret that a commitment in Texas has made it impossible for Senator Bentsen to appear personally before the subcommittee. He had requested that he be able to introduce his distinguished fellow Texan and our next witness. He has given me a statement, however, to enter in the record, and I gladly include it there.

[The prepared statement of Mr. Anderson follows:]

STATEMENT ON BEHALF OF M. D. ANDERSON HOSPITAL

Senator **BENTSEN**. Madame Chairman and distinguished members of the Subcommittee on Investigations and Oversight:

I regret that a long standing commitment in Texas makes it impossible for me to appear personnally before the Subcommittee to introduce Dr. Charles LeMaistre, a distinguished fellow Texan who is President of the University of Texas System Cancer Center, which includes M. D. Anderson Hospital and Tumor Institute in Houston.

However, I appreciate this opportunity to commend you and your Subcommittee members for focusing public attention on some of the important problems and dilemmas associated with the treatment of cancer. Cancer strikes a particular terror in the minds of millions of Americans. All of us, Madame Chairman, have a friend or relative who has suffered from this disease. We have seen the pain that cancer can cause, and we can appreciate the feeling of despair when it has crossed the threshold of treatment and death becomes inevitable.

I need not tell the members of this Subcommittee that dramatic progress in treating many forms of cancer has been made over the last decade. Much of this progress is directly attributable to the talent and dedication of American researchers and physicians. As you have pointed out, progress in our campaign against cancer also requires a willingness to test new frontiers of medical science. While no one questions the importance of pressing forward with the effort to treat cancer more effectively, we also recognize the importance of proceeding responsibly and exercising every caution in areas such as chemotherapeutic research and treatment.

In Texas we are proud of the fact that the University of Texas M. D. Anderson Hospital is one of the premier comprehensive centers in the nation. Some 30,000 patients are treated at M. D. Anderson each year; one quarter of them from outside the state of Texas, many of them from abroad.

About half of these patients, Madame Chairman, will receive anti-cancer drugs and many of them will benefit from recent break-throughs in chemotherapeutic treatment. Thirty-five to forty percent of those treated will be cured, yet only a few short years ago many of these individuals would have had no prospect for recovery.

As Dr. LeMaistre will inform the Committee, M. D. Anderson fully recognizes its responsibilities in the area of experimental research and has instituted an internal control system to insure that institutional rules and guidelines for clinical investigation are in place and adhered to by staff physicians and scientists.

In closing, I would like to stress that M. D. Anderson has made enormous contributions to medical science and has treated hundreds of thousands of cancer patients without undue reliance on federal funding. Less than 10 percent of M. D. Anderson's income is derived from federal sources. Forty percent is state funding, approximately 40 percent is paid by patients through fees, and the remaining 10 percent is generated through private contributions. I think you will agree that this linkage of private and public support is a record to be proud of.

Dr. LeMaistre, who will testify before the Subcommittee, has an outstanding, 15 year record of service in the administration of academic health science centers and universities. He is ably assisted by Doctors Bowen and VanEys who accompany him today. Again, Madame Chairman, I want to thank you for the opportunity to make a few introductory remarks on behalf of these distinguished gentlemen.

Senator **HAWKINS**. The University of Texas system includes M. D. Anderson Hospital and Tumor Institute in Houston. We will ask Dr. LeMaistre to introduce his associates.

STATEMENT OF CHARLES A. LEMAISTRE, M.D., PRESIDENT, THE UNIVERSITY OF TEXAS SYSTEM CANCER CENTER, ACCOMPANIED BY JAMES M. BOWEN, PROFESSOR OF TUMOR VIROLOGY; AND JAN VAN EYS, HEAD, DEPARTMENT OF PEDIATRICS AND CHAIRMAN, INSTITUTIONAL REVIEW BOARD

Dr. **LEMAISTRE**. Thank you, Madam Chairman. I thank you for allowing me to testify here today. I am Dr. Charles LeMaistre, president of the University of Texas System Cancer Center, which includes the M. D. Anderson Hospital and Tumor Institute.

I appreciate the opportunity of sharing in this open hearing our thoughts and comments and to have the opportunity to answer your questions. With me is Dr. James M. Bowen, who is on my right. Dr. Bowen is professor of tumor virology and associate vice president for research. Dr. Jan van Eys, head of our pediatrics department and chairman of our institutional review board, is on my left. I have asked them to join me today because they have the responsibilities for clinical investigation, for protection of human rights, and for administrative procedures that govern our research program. These are three of the topics that Mr. Michie had advised me that this subcommittee was interested in.

These topics with comments directed particularly toward improving the processes that you requested, Senator Hawkins, are addressed in the written statement. If I may just outline the topics in the written statement, and then I would like to have one brief opening statement.

We cover in that written statement the concept of phase I as we apply it at our institution. We state very clearly, I hope, the institutional procedures governing clinical investigations because it is apparent to me from the testimony this morning that they are badly misunderstood.

Another subject addressed is the MTHHF incident. You will notice there is an appendix to our submission. The purpose for this is to clarify for the record exactly what happened. I think there is much confusion. The appendix also has been submitted to the House of Representatives with regard to testimony that occurred there in recent weeks.

The third area in the written statement are changes in procedures that occurred as the result of MTHHF. We also address the chronologic steps for the Institutional Review Board's procedures and how they are approved.

The fifth item, one we feel very keenly about, is informed consent. You will notice that in appendix E there is a model or a guide. This document is provided to investigators to give them an outline of those things that they must attend to in the process of developing an appropriate specific one for investigation.

The sixth area, as I mentioned, will be devoted to recommendations for improving the process, particularly at the Federal level.

We are very proud to represent the physicians of the U.T. M. D. Anderson Hospital today. We believe these to be the hardest working, most dedicated human beings we have been associated with. They clearly could work in other places where there is considerably more joy and where the pressure of peer scrutiny is far less. I think most physicians enter the field of oncology because they are compelled to contribute toward understanding of one of the greatest enigmas that has ever confronted mankind.

One point I want to make very clear. The institution we serve is State-funded, created by the people of Texas in 1941 at a time when many thought cancer to be hopeless; 165,000 patients have been served since then. We see approximately 30,000 patients now each year. About 15,500 of these will receive anticancer drugs.

Although research and teaching at our institution are present and highly regarded, our highest mission priority is patient care.

At M. D. Anderson we believe the primary objective of any clinical investigation involving a new drug must be an attempt to treat the patient's cancer. Our phase I studies are primarily designed to determine the appropriate, effective dose which can be given safely and to ascertain its toxicity. There have been many instances at our institution in which phase I drugs have extended the lives of our patients.

The procedures governing clinical investigations at our institution are complex, but they are not static. They are being constantly improved. The rules and procedures are imposed on us by Federal regulation, by State statute and, most importantly, by ourselves. This is as it should be, in our opinion. We feel that these guidelines help insure the scientific integrity of our process. But paramount above all else, the guidelines protect the rights of the patients who place their trust in us.

Approaching this distinguished building this morning, I have to admit that it occurred to me how much more appropriate it would be to have these hearings in a comprehensive cancer center. There are many things we cannot demonstrate to you here that we could in that setting. The entire sequence of the development from basic scientific knowledge as it moves through the channels of the institution to its application at the bedside is a very thrilling thing that you should see.

I think the correct perspective of clinical investigation could be more easily understood, primarily because we would see concerned, passionate and talented physicians who are working to find answers for patients where there are none, particularly as this regards phase I drugs.

Even more to the point, the functioning of informed consent as it is practiced beyond the informed consent document could become apparent to you.

Senator Hawkins, we would welcome the opportunity to host you or your subcommittee collectively or individually at any time.

May I cite one example that I believe would elucidate informed consent? We believe that the appropriate informed consent document is only the beginning of our obligation. Complete understanding by the patient is our goal. To that end, 2 years ago we began a patient education program that has produced 111 different publications with another 25 currently in publication. Our educational materials, which are in addition to those we provide patients from the National Cancer Institute and by the American Cancer Society, are designed at our institution to enable us to afford individual instruction to patients.

Our aim is very simple. It is to reduce fear through understanding of the disease and its treatment, permitting each patient a more objective assessment of the options available for treatment including new investigational drugs. Classes are actually held on all days of the week for new chemotherapy patients.

Let me show you some examples of the kinds of materials that we use. We brought a sample of these with us today. There is a packet that is given to every patient in phase I or phase II, III, or IV or any other form of treatment that contains information about chemotherapy that explains chemotherapy: The notice of the classes and other information that is needed to begin the understanding that relates to the chemotherapy.

There are at least two departments that have now completed their booklets. A handbook was produced by my colleague to the left for the parents of pediatric patients. It takes them through the entire sequence of the treatment of cancer, even including the names and telephone numbers of the doctors involved who may be called at any time. This roster of topics listed here is a very complete one that does correctly inform the parent of how they may effect and afford all of the facilities to the benefit of themselves and of their child.

There are other documents that deal directly with cancer itself because we believe the beginning of the education process relates to the understanding necessary of the cancer that the patient has.

Should the conventional chemotherapy fail patients who are beginning this educational process, they may indeed become candidates for phase I trials. If so, these patients will have a much better understanding for the informed consent document. And this is a part of our purpose in the educational program.

Madam Chairman, I am sure that you agree that our overriding goal in these hearings and in our purpose in testifying before you is the ultimate elimination of cancer as a major health threat in our society. Our disagreements, our mutual efforts to improve the process, should not be obscured or impede in any way our ultimate achievement of that goal.

I want to particularly commend you in your opening statement and Senator Kennedy in his eloquent statement earlier this week in confirming that point to those of us that are here this morning.

Thank you. If you have questions that we may answer, we would be delighted. My colleagues will join me, if you permit, in the answer to these questions. These are the people that are actually responsible for the areas that you are most concerned about. Thank you, Madam.

[The prepared statement of Dr. LeMaistre follows:]

Statement of

Charles A. LeMaistre, M.D.

President

The University of Texas System Cancer Center

Senator Hawkins and members of the subcommittee, I thank you for allowing me to testify today. My name is Charles LeMaistre and I am President of The University of Texas System Cancer Center, which includes the M. D. Anderson Hospital and Tumor Institute at Houston. I appreciate the opportunity to appear in this open forum, share with you my thoughts on the nation's anti-cancer drug development program, and answer your questions. With me are Dr. James M. Bowen, Professor of Tumor Virology and our Associate Vice President for Research; Dr. Gerald P. Bodey, Professor of Medicine and Director of our institution's Office of Protocol Research; and Dr. Jan van Eys, Head of our Department of Pediatrics and Chairman of our Institutional Review Board. I have asked them to join me today because they have responsibility for clinical investigation, protection of human rights, and administrative procedures governing research, the three areas which Senator Hawkins' staff has told me are of special interest to the subcommittee. Each of my colleagues is prepared to receive questions, should you care to address any to them. (Biographical data are provided in Appendix A.)

I spent the early years of my career on the faculties of three medical schools and have devoted the last 15 years of my professional life to administration in academic health science centers and public universities. Today, I am representing the U.T. M. D. Anderson Hospital, which I have had the privilege of heading for three years. M. D. Anderson is among the nation's largest centers devoted exclusively to cancer patient care, research and education. Dr. Bodey, Dr. Bowen, and I are on the staff of an institution with a singularly ambitious and important mission: the ultimate elimination of cancer as a significant health threat.

We represent the physicians of M. D. Anderson Hospital, who I believe are among the hardest-working members of the medical profession and the finest human beings I have ever worked with. They could work in other places where there is considerably more joy and the pressure of peer scrutiny is far less. I think most physicians enter the field of oncology because they are overwhelmed with the horror of cancer and are filled with a deep sense of compassion for those who are struck by the disease. They are in the field because they are compelled to contribute toward understanding one of the greatest enigmas that has ever confronted mankind.

I will not attempt to describe to you the devastating consequences of cancer in terms of human suffering or financial impact, for I believe this has been made plain to you in prior testimony, if not through personal experience. Nor will I try to chronicle the achievements of my colleagues at M. D. Anderson or the extraordinary variety of innovative research under way there, for that was not your purpose in inviting me here to testify. Rather, I will limit my remarks to discussing the much-maligned process of developing new anticancer drugs and reviewing how this painstaking task is carried out at the U.T. M. D. Anderson Hospital -- a procedure similar to those found at other cancer centers and medical schools throughout the nation. In contrast to a number of distorted explanations of how new anti-cancer drugs are developed, I would commend to you the cover story in the November 2, 1981, issue of Newsweek, which I think does a superb job of summarizing progress made in recent years in the field of cancer chemotherapy (see Appendix B).

Approximately 30,000 people with cancer will be cared for at M. D. Anderson Hospital this year. Of these, about 15,500 will receive anti-cancer drugs, either with surgery and/or radiation or as the sole treatment for their disease. Enough progress has been made during the past decade so that some cancer patients can now be cured with chemotherapy. Unfortunately, for many patients with common tumors such as lung and colon cancers, we have not found the anti-cancer drugs that are as effective as we need. Additionally, many patients who respond initially to conventional chemotherapy will develop recurrences as their tumors become resistant to this treatment. All of these patients will die of their cancer unless new, effective therapy is discovered. These are the patients who participate in studies of investigational drugs.

At M. D. Anderson, we believe that the primary objective of any clinical investigation involving a new drug must be to attempt to treat the patient's cancer. Questions have been raised about the primary objectives of Phase I investigations of new drugs. From long experience with complex laboratory and animal studies, we are acutely aware of the shortcomings of these studies in predicting human toxicity. Anti-cancer drugs are not selective in killing only cancer cells; they also kill some normal cells. Consequently, few anti-cancer drugs are without toxic side-effects. A major objective of the initial Phase I study of a new drug is to determine the appropriate dose and ascertain its toxicities. The appropriate dose which is likely to destroy the patient's tumor will usually have major side-effects.

It is a naive misconception to assume that patients taking part in Phase I investigational programs are robust individuals -- or even that their cancers have been arrested. In fact, they are most often people who have failed to respond to all conventional forms of treatment. They are usually desperately ill people whose cancers are out of control. They are most often people without established treatment options whose only other option is certain death.

It is true that the maximum therapeutic efficacy of a drug cannot be defined solely on the basis of a Phase I study because evaluation of safety must come first. Also, the numbers of patients included in these studies are small and the types of their cancers vary greatly, so it is difficult to draw conclusions. But, even at the Phase I level, the physicians at M. D. Anderson are always looking for drug activity that will help the patients participating in the study --and there have been many instances in which Phase I drugs have extended the lives of the patients involved.

My point is this: All cancer chemotherapy that is conventional today was experimental at one time, and that time was usually only a few years ago. For the past 15 years, M. D. Anderson has played a major role in investigating many experimental drugs that are standard now, a role that has earned for our physicians a well-deserved reputation as leaders in cancer chemotherapy and antibiotic therapy. M. D. Anderson doctors contributed important observations that led to the introduction of several conventional anti-cancer drugs, including:

-- Vincristine, an important drug for the treatment of leukemia and lymphoma;

--Adriamycin, one of the most active anti-tumor drugs, which is used to treat adult acute leukemia, lymphoma, lung cancer, breast cancer and bone tumors;

--Bleomycin, which in combination with other drugs can cure testicular cancer;

-- and many more.

Given the current state of scientific knowledge, drug therapy continues to represent one of the most promising avenues for controlling systemic or advanced cancers. Consequently, evaluation of new, potentially effective antitumor agents continues to be an endeavor of high priority at M. D. Anderson Hospital.

It is to the meticulous manner in which that endeavor is pursued at M. D. Anderson Hospital that I now would like to direct my remarks. The procedures governing clinical investigation of new drugs at our institution are both considerable and complex. And they are not static because they are constantly being improved. Guidelines are refined, terms of compliance are altered and new rules are implemented as our body of scientific knowledge advances and society's expectations change. These rules are imposed upon us by Federal regulation, by State statute and, most importantly, by ourselves. This is as it should be, because guidelines help insure scientific integrity and -- paramount above all else -- guidelines protect the rights of the patients who place their trust in us.

The soundness of M. D. Anderson's institutional procedures governing drug studies was recently questioned because of an incident involving an investigational drug, 5-methyltetrahydrohomofolate (MTHHF). Small tracer doses of the drug were administered to six patients at M. D. Anderson several months before MTHHF was approved for Phase I human testing by the U.S. Food and Drug Administration. This inadvertence was a procedural error and not an error of intent on the part of the investigator -- a distinction that is important, but one that has been obscured in testimony before the United States Congress. (A thorough discussion of this testimony is provided in Appendix C.)

Events leading to the error actually began several years ago. Studies had shown that MTHHF was active against experimental tumors resistant to methotrexate (a standard anti-cancer drug) and had relatively low toxicity in animals. Based upon this evidence, a protocol for Phase I studies of MTHHF, including accompanying clinical pharmacology studies, was written by M. D. Anderson clinical scientists in May 1978, and approved by our institutional review board in September 1978, pending final authorization from the NCI to commence. In early 1980, the scientist assumed -- but did not seek to confirm -- that the drug had been approved for Phase I testing. He then began the preliminary pharmacology study, administering very small doses of MTHHF to six patients to determine the drug's pharmacology.

Let me emphasize two points: First, more than two years elapsed between May 1978, when scientific evidence demonstrated that the drug was worthy of testing in humans, and December 1980, when it was finally approved for Phase I testing by the FDA. Second, the M. D. Anderson Phase I protocol for MTHHF was never implemented.

The error regarding MTHHF was discovered because the scientist submitted his work for peer scrutiny at the 1981 meeting of the American Association for Cancer Research. His violation was spotted by an official of the NCI in the book of abstracts published for the AACR meeting and was reported to our Executive Vice President by telephone on June 16, 1981.

After a preliminary review by my staff, I formed an ad hoc hearing committee on June 18, 1981, to investigate allegations and make recommendations for action. Under the chairmanship of a widely respected physician who is not a member of the M. D. Anderson staff, the committee examined evidence, took testimony and made their recommendations in a report to me on June 25, 1981.

The committee found that M. D. Anderson's rules on investigations involving humans had been violated, although without intent and with no plan by the scientist to deceive either the institution or the National Cancer Institute. A complete medical audit of the six patients, conducted by the audit committee of our medical staff, concluded that no harm came to them as a result of receiving the drug. The ad hoc committee also found that informed consent had been obtained, but questioned its adequacy. Although a specific, detailed consent document had been developed for the proposed Phase I study, the scientist did not use this form for his pharmacology study. Furthermore, he used outdated forms now considered inadequate.

The committee made a number of recommendations for disciplinary action against the scientist, who is a highly valued investigator with more than 30 years of significant contributions to anti-cancer drug development. Among other actions, the committee recommended that he be formally censured, barred from participating in any studies involving human subjects and relieved of his responsibilities as principal investigator on grants and contracts involving human volunteers. I concurred with all the committee's recommendations, notified the scientist in writing on June 30, 1981, then reported these actions to the Director of the National Cancer Institute both by telephone and, subsequently, in a letter dated July 1, 1981.

All these actions took place before the arrival of the NCI site visit team on July 13, 1981, an investigation with which we cooperated fully. NCI's final report of its conclusions and actions was transmitted to us on August 18, 1981. As a postscript, I might add that NCI, in what I believe to be a rare action, also issued a press release on August 20, 1981, summarizing its actions. M. D. Anderson distributed the statement to our local newspapers while it was simultaneously released in Washington by the NCI.

Now, I would like to return to the actions of the institutional ad hoc hearing committee we established and comment upon one area of their activity that I failed to mention earlier. In addition to examining the incident governing MTHHF, the committee was ask[illegible] review all M. D. Anderson's institutional procedures regarding Phase I investigations. Their ultimate conclusion was that sufficient institutional rules and guidelines were in place and operating to prevent such an incident, had those rules been followed.

As I stated before, the MTHHF incident clearly departs from the acccepted institutional procedures that were in force at that time, hence the harsh punishment rendered to an established scientist. Nonetheless, I ordered a major review and reorganization of our clinical research process to guarantee that a similar incident will not happen again and to insure that all our staff fully appreciates the rules process under which they may conduct clinical research. The reorganization resulted in several changes that we believe substantially strengthen the administration of our clinical investigations, including:

-- Creation of an Office of Protocol Research to work with investigators in the design of their protocols and assure compliance with all Federal, State and institutional guidelines;

-- Maintenance of all permanent records of informed consent within the Office of Protocol Research;

-- Development of clearly written, revised policy and procedure documents for distribution to all staff;

-- Strengthening of controls regarding release of drugs from the pharmacy; only upon authorization of the Director of the Office of Protocol Research after all institutional and federal approvals have been obtained may the investigational drugs be released.

May I briefly review our current institutional procedures regulating clinical protocols and informed consent, for they are of importance in the prevention of a recurrence of an MTHHF incident. Our institutional procedures were apparently not correctly understood in previous testimony (see Appendix C).

The first step in a clinical study with an investigational agent involving patients at M. D. Anderson Hospital is the preparation of a written protocol and the simultaneous development of an appropriate informed consent document.

The approval process begins with the investigator's submission of a proposed protocol to the departmental chairman for scientific review by peers within his or her department. If the protocol is approved at the departmental level, it is signed by all the investigators and is then submitted to M. D. Anderson's Office of Protocol Research. This office reviews the design and content of the protocol, insuring that adequate information is available for a successful NDA or IND application and that the consent document is appropriate in terms of information needed by a patient for understanding of the clinical investigation to be conducted.

If approval is received from the Office of Protocol Research, the protocol advances to the 17-member institutional review board, which is charged with analyzing each proposal to insure protection of the rights of the patients participating. At M. D. Anderson, this committee is composed of eight staff physicians (including one who also is an attorney), a nurse, child psychologist, and chaplain. The remainder of the committee includes representatives from various segments of the community, including a businessman, homemaker, attorney, university biology faculty member, a pediatrician who is a noted medical ethicist, and a staff member from the local chapter of the American Cancer Society. (A roster of M. D. Anderson's IRB -- known as the Surveillance Committee -- is provided as Appendix D.)

Concurrent with submission to the IRB, the Office of Protocol Research submits the protocol to the source of the investigational agent (the NCI, a pharmaceutical firm or the FDA). In the vast majority of studies at the U.T. M. D. Anderson Hospital, the permit to hold the agent is filed by and approval is gained through the NCI or the pharmaceutical firm. It should be re-emphasized that the evaluation of the protocol by the NCI or a pharmaceutical firm takes place simultaneously with scrutiny at M. D. Anderson. Our institutional policy requires that investigational agents may be kept only in our pharmacy and may not be released from the pharmacy until notified by the Director of the Office of Protocol Research that IRB approval has been obtained and an IND granted.

Procedures for pharmacology studies in force at the time of the MTHHF study were slightly different. A specific protocol was prepared for every pharmacology study, either as a separate protocol or as an addendum to the Phase I or II protocol detailing all procedures to be followed. We have altered the procedures to require that all pharmacology studies using investigational drugs in humans follow exactly the same procedures as Phase I protocol proposals. If the protocol involves the administration of radioactive materials, the protocol is submitted automatically by the Office of Protocol Research to the Radioactive Drug Research Committee for simultaneous review. This committee has FDA approval to provide a local IND under specific circumstances. Regardless of this committee's action, a protocol cannot be implemented until it is approved by both the IRB and the agency providing the drug and holding the IND. The Office of Protocol Research has the responsibility to assure that all investigational drug protocols have had the proper approvals and that all safeguards are in place before the protocol is implemented.

Every clinical protocol at M. D. Anderson requires informed consent from each patient who volunteers to participate in a study. There are no exceptions. These documents are reviewed and approved by the IRB as a part of the final protocol. Institutional policy requires that the physician caring for the patient or one directly involved in the investigation must discuss all aspects of the study with the patient, then secure the patient's signature on the informed consent document. The basic elements of the informed consent document are tailored to the individual investigation so that the patient has in written form: (1) an explanation of the purposes of the research; (2) a description of any reasonably foreseeable risks or discomforts; (3) a description of any benefits the subject may reasonably expect; (4) a disclosure of any alternative courses of treatment, if any; (5) a statement regarding the extent of confidentiality of records; (6) an explanation of whether compensation or treatments are available should injury occur, if the risk is more than minimal; (7) an explanation of whom to contact for information regarding the research, subjects' rights or research-related injury; and (8) a statement that participation is voluntary and that the subject may discontinue participation at any time. (A "model" informed consent document to serve as a guide for investigators is attached as Appendix E.)

It should be emphasized that at the outset of Phase I studies all side-effects may not be known and our patients are so informed. When evidence exists to indicate that a specific side-effect is likely to occur, the informed consent document should specifically include that information. Let me stress, however, that we view the content of the document, no matter how detailed or carefully drawn, as only the first important step. The second important step is the responsibility of the physicians to explain the full consequences of the investigation in an understandable and candid, but compassionate manner.

Senator **Hawkins**. Thank you so much, Dr. LeMaistre.

I know you have worked to insure appropriate informed consent. Can you give me your assessment on any problems that still exist in informed consent?

Dr. **LeMaistre**. Madam Chairman, may I turn to the chairman of the institutional review board to know that, primarily because I hope he is well prepared on that topic.

Dr. **van Eys**. If you allow me, Madam Chairman, I am Dr. Jan van Eys, the chairman of the IRB. I have been chairman of the IRB at the M. D. Anderson now for 4 years.

There is a very basic problem in the IRB process that is a very understandable consequence of the problems in the endeavors that we are addressing. Most simply stated, it is as follows. When I am well, I want the problem, cancer, solved. When I have cancer, I want to be cured. Now, solving the problem, cancer, is the concern of the FDA, the NCI, Congress. But, when you have cancer and you come to an institution, you have a concern between physician and patient. Most of the regulations as they now exist address solving the problem of cancer. And they are not always immediately translatable to the interaction of the patient who desperately wants something done.

It is the very difficult task of an IRB to bridge that gap to the best way they know how.

It would be, in the eyes of our institutional review board, the height of callousness to allow a researcher to do a phase I study purely for the purpose of toxicity and pharmacology in a patient who is as desperate as a cancer patient who has reached the phase I drug odyssey. On the other hand, it is our sincere understanding that a patient is not dying unless that patient has decided that the dying process is ongoing. We cannot do psychological euthanasia any more than we can do physical euthanasia.

Therefore, when the patient says, do you not have something, then it is the task of the IRB to be very sure that the phase I drugs that our researchers in fact, want to offer, do in fact have a modest and a very small modicum of promise. Some patients, if they are adequately informed, say that is not worth it. A few patients say a one-in-a-million chance is something I absolutely want to take. We do not think that those patients are misled. A one-in-a-million chance is to them all the chance that they have. They feel like—you know, a thousand fall on my right side and a million on my left, but nothing will come to me; I will be that one in a million.

The nature of informed consent is that we give the facts and that the patient has the dignity to decide what the consequences are of the options offered and that the patient will, in fact, select those options that are best in his or her feelings.

Unfortunately, there are a great deal of feelings on both sides, feelings generated by a horror that a phase I drug can, in fact, inflict, unknown before this actually happens, before we know what the side-effects are, and then in hindsight say that patient ought not to have done that. But that is taking away the dignity of the patient for making that decision at the time they made that decision.

Of course, the IRB has to be very careful that all side-effects known are given, that all side-effects that are beginning to be learned in the process of a phase I drug testing are told to the patients who are already receiving it, and then learned-of side-effects. The process has to be monitored. All those things are absolutely necessary. It is a very difficult task. But to say that the phase I drug is purely experimental without any hope to the patient, I do not think our IRB ought to allow such research going on.

I hope I have addressed your question.

Senator **HAWKINS**. Yes, thank you.

Dr. **LEMAISTRE**. Madam Chairman, may I comment upon the topic?

Senator **HAWKINS**. Surely, Dr. LeMaistre.

Dr. **LEMAISTRE**. I think there are several things that we have learned from the MTHHF experience that are recorded in our written testimony, and I will not touch to those because they are clearly outlined as our response on what we now know to be problems and problems that may be present in other institutions.

There are other areas, however, that I think we should list for you, at least three, that reach beyond what we have done and perhaps what any other institution has been able to do in this regard.

One is the problem from the perspective of an institution such as ours in complying with the requirement of the informed consent document from a legalistic standpoint as it has evolved at the Federal level. I have asked Dr. van Eys to chronicle for me the recent history of the development of our informed consent over the last several years. And it is a very revealing reaction to constantly changing and clarifying and improving suggestions and recommendations from the Federal agencies, which we are grateful for. But only this last July was there reconciled between the NCI and the FDA the regulations regarding informed consent. And we complied with the draft regulations, I believe, in January 1980, and with the regulations as issued this July. There needs to be more coordination of this type and more interchange between the institutions.

The reason that I feel this very strongly are twofold. One, we are forced to violate our informed consent document. Please note in appendix E, the model for our informed consent document, section 9, where we deal with confidentiality. The institution, through its physician doing the investigation commits to that patient that his or her name will not be revealed nor will there be a revelation of any other confidential data. We make that promise. We cannot always explain how the information appears in public circumstances.

My point is very simple on this particular point. We are writing, as you have requested these previous persons testifying, to err on the side of trying to protect the patient. We do this in phase I. If there is any doubt whatsoever as to whether something occurring is a toxic manifestation, we err in reporting it as such although we may have some doubts. At the beginning of a phase I study, we cannot always anticipate what the toxic effects are, and we tell our patients this.

On the other hand, our reports that come forward are slanted, primarily to alarm and to alert—perhaps alarm—those at the National Cancer Institute that we cannot tell whether this is toxicity or not. That is the nature of the information that occasionally is being released that gets the relationship of the drug, the patient, and the physician out of perspective.

Also, I feel that there are very good and valid mechanisms for the release of confidential information that should be followed by Federal agencies as well as by individuals. And I simply say I have no way of knowing how information from our institution is made public in this area except that it obviously is occurring with the names of the patients and indeed with, in one instance, the publication in the newspaper of a death certificate, I believe.

Now, the last point I would make goes back to a point I made earlier. We have not yet completed our perfection of the educational process by which we address the needs of the patient to understand cancer, remove their fear, and then to develop a communication with the physician so that they may know as much as we can possibly tell them about the disease, its treatment, and the consequences of the treatment.

There is a second phase that perhaps has been alluded to in your earlier testimony. It was not this morning, I believe. And that is that we need to be sure that our physicians doing clinical investigation not only are competent, which we check them for very carefully, but also to be absolutely certain that they can communicate adequately with our patients. We find at times the intent to do so is there but the language that is used is sometimes imperfect in communicating real understanding. As a teacher all of my life, I believe very firmly that our goal is learning. And in this instance through the informed consent—not the document but through the informed consent process—our goal is learning and understanding by the patient.

So, those three areas, Madam Chairman, I think, have been underdeveloped at our institution and others. We earnestly seek cooperation in achieving further reconciliation of difficulties in all three areas.

Senator HAWKINS. That is most important. We had some testimony here Tuesday from parents who had not been told by the doctor all of the consequences or all the information that was available at that time of the drug they were going to treat the child with. They felt maybe that had been protection for them. But the parents themselves said that, once you have been told you have cancer and it is terminal, there is no need to protect them from any other bad news; that is the worst news you can possibly have.

There are some physicians that feel that you give that bad news but then you must protect them from the next step. It was the parents' wish that the informed consent contain all the information and the potential problems and that the physician can relay this information to the patient or the patient's parents or relatives in language that is understandable to both parties, so that everyone does understand what is being said. In many instances the doctor does not have the information; our hearings have discovered that. So, maybe there should be a form in which the doctor can state that he is telling all he knows. If evidence comes out later that this was available but not disseminated to him, I think the doctor has the protection by himself that he has told all that had been given him to tell. You may want to think about that as you are developing and constantly updating informed consent. I think that should not stay static. It should be constantly fine-tuned with the communication network that we now have in place.

Dr. LeMaistre, it came to our attention that M. D. Anderson was the subject of a site visit report conducted by a monitor from the NCI on May 13 of this year. The purpose of that site visit was to evaluate the adult cancer treatment evaluation program protocols sponsored by NCI. Are you familiar with that visit?

Dr. **LeMaistre**. I am not sure which one you are referring to.

Senator **Hawkins**. May 13.

Dr. **LeMaistre**. May 13?

Senator **Hawkins**. By the NCI.

Dr. **LeMaistre**. We have a site visit on MTHHF on July 13. Could that be possibly the date?

Senator **Hawkins**. This is the annual site visit May 13 by the contractor monitor.

I believe we have given you the document. We have given you a copy of the annual site visit report signed by the contractor monitor.

[The information referred to follows:]

ANNUAL SITE VISIT REPORT

Investigator: Dr. No. 1, principal physician-investigator.
Location: Comprehensive Cancer Center.
Date: May 13, 1981.
Monitor: Contractor monitor (for NCI).

On May 13, 1981 I visited the Comprehensive Cancer Center to conduct an annual site visit on the Adult Cancer Treatment Evaluation Program protocols, sponsored by NCI. These protocols are: No. 1, 2, 3, and 4. Protocol No. 5 has recently been activated also, but no patients have yet been entered.

I met with Dr. No. 2, an internist with responsibility for the Data Management Office. It appears that, although a clinician, he has acted as prime organizer and expander of the Data Management System used in the development therapeutic clinic. He noted that they had recently expanded this activity into the Gastrointestinal Clinic. It will be in this clinic that protocol No. 5 may be started. He noted that the Cancer Center is an institution which is sadly lacking in computer services, with only lab data being readily available in automated fashion. He has recently instituted links with Epidemiology and hopes to expand this to include all registration and demographic data for patients on study protocols. He understood that there were problems in collecting data on protocol, No. 3 and No. 6, but felt that he was unable to help in any way, as these studies are being conducted in a site remote from his Data Management System. It appears that Dr. No. 3 supervises these studies with the aid of a research nurse and his Data Management Office does not receive any detailed raw data, except for simple registration information. I told him that I would later discuss this matter with Dr. No. 1.

I then talked with person, who is head of the Data Mangement Office, supervised by Dr. No. 2. We reviewed the monitor's reports and she stated that she found these extremely helpful and would like to see them available on a regular basis. I left the April 30, 1981 report with her. I asked her about the system for obtaining interim counts obtained by patients from their own physician. She recognizes that this is a problem but they do have, ongoing, attempts to remedy or improve this deficiency.

I visited the pharmacy and met with pharmacist, the pharmacist responsible for investigational and new drugs. In response to my enquiry she noted that a new procedure had recently been instituted, whereby the pharmacy maintains a list of NCI approved protocols and their number. Each physician prescribing an investigational new drug for an NCI approved study is required to write the protocol number beside his signature, otherwise the prescription will not be honored. Lists are maintained on the data sheets, also, of authorized prescribers. Monthly reviews of all prescriptions for investigational drugs are carried out and a mechanism is available for follow-up of unauthorized signatures. In the first instance the pharmacy forwards a letter to the principal investigator, asking if the unauthorized signature had been authorized by the principal investigator to prescribe drug or medication. If the answer by the principal investigator was in the negative, a letter of reprimand is issued to the department head, supervising the unauthorized prescriber. There is not specifically a central inventory or Dispensing Log. There is, however, a record kept of all investigational new drug prescriptions dispensed. Gross accounting for supplies on hand is also undertaken. It should be possible to reconcile these two record sets and arrive at a close although perhaps not perfect accounting for drug supplies used.

I then met with Dr. No. 4, one of the principal investigators, intimately involved with drug study No. 1. Dr. No. 4, on this occasion, was extremely pleasant and helpful, unlike my last visit where he was defensive and irritated by my questions. He noted that following conduct of the study, standard grading, criteria had been adopted for toxicity and physicians were now required actively to grade such data. A copy of the criteria is attached. He also noted that new flowsheets with visit orientation had been issued and were in use in the Gastro-intestinal Clinic. He has moved from the Department of Developmental Therapeutics to the GI-Service, where he is continuing his interest in investigational drugs. He noted that there were attempts to improve the data collection system, with cooperation from the Data Management Office supervised by Dr. No. 2. He felt that attempt to obtain interim blood counts by pressure on the private physician supervising the outpatient treatment, would improve the quantity and quality of data available.

Finally, I interviewed No. 1. In going over the checklist, it was evident that he understood the need for Institutional Review Committee approval and that copies of such approval were available. He noted that written informed consent was always obtained, but that the forms were kept in the patients' chart. He understood the need to follow the protocol in detail and shared his feeling that protocols were frequently overwritten. He observed that on the day following my visit, there was to be a meeting in which the standard structure of protocols was to be reviewed. He understands the need for the classificiation and prompt reporting of adverse experiences and the need to follow up on dropouts. He is familiar with regulations as they pertain to record keeping and record retention. Laboratory normal ranges have not changed in the last twelve months. He is aware of the need for test article accountability and felt that the pharmacy was discharging its responsibility in this regard. He was also aware of the need for the principal investigator to personally check data and observed that he would never knowingly allow anything dishonest to occur.

Discussion then focussed on the question of the lack of data supply for protocols No. 3 and No. 4. It appears that 49 patients have been entered onto Protocol No. 3 and 17 patients onto No. 4. He is adamant that he has an understanding with NCI that he will not be required to supply data on unfunded NCI studies, even where NCI supplies the investigational drug. He maintains that this agreement was recently reviewed with NCI Dr. in conversation and it is his understanding that this arrangement remains in force. He feels that unless NCI agrees to provide additional funds, he must maintain this posture. He quite clearly did not like my raising the subject of compliance with the federal regulations and stated that he had no time for the FDA. It does not seem at all likely that Dr. No. 1 will initiate data submission on these two protocols, without further action from NCI. If NCI is truly in agreement with Dr. No. 1 that they do not require data submission on NCI approved protocols on investigational drug supplied by NCI, where these studies are unfunded, then such studies should not be forwarded to the Clinical Trials Monitoring Service for monitoring and data collection. If, however, NCI is not truly in agreement with Dr. No. 1 in regard to his stance about data collection on these unfunded studies, then the approval of such studies and supply of investigational new drugs to this institution should be reviewed.

(signed by Contractor Monitor).

Senator HAWKINS. During that site visit the monitor encountered one of the physicians at M. D. Anderson who is involved in the administration of experimental chemotherapy. In response to the monitor's inquiry, this physician indicated he had an understanding with the National Cancer Institute that he would not be required to supply data on studies where the National Cancer Institute supplied the investigational drug.

Do you have personal knowledge of such an agreement?

Dr. LEMAISTRE. No, Madam Chairman, I do not. May I ask Dr. Bowen if he has such knowledge?

Senator HAWKINS. Surely.

Dr. **Bowen**. Madam Chairman, I had an opportunity to see briefly and superficially this document. I believe it is the same one that was available on Tuesday at the hearings. Since administration had not seen that document before and we had not been, as administrators, informed of that incident, I went back and interviewed some members of our clinical investigation staff, putting questions to them about that report.

I can only give you my understanding of their position on that. But, if you will accept it just as my understanding and impression, I will give you the account of my discussion.

The issue that was in disagreement, if that is the word, relative to that reporting posture was not that our investigator did not want to report those data. Those studies were studies conducted under a grant. That same group also were working under an NCI contract. What had been requested of our investigator, according to my discussion with him, was that they put that grant-supported study into the program where they were reporting all clinical data on a twice-per-month basis.

The investigator became alarmed at that because they were not funded to do reporting that frequently on that particular study. They had already agreed to make the twice-monthly reports on the contract program but felt that they were not sufficiently funded or staffed to make the two reports on the grant-supported study. However, our investigators maintained that they did not say that they had no obligation to report their data to the NCI. They did comply and state their willingness to comply in the future with data reporting, but they did challenge the twice-monthly reporting posture of grant-supported studies as opposed to those on the contract for which they were supported for that kind of reporting.

Senator **Hawkins**. In addition, your physician indicated he did not like discussing the subject of compliance with Federal regulations, and he had no time for the FDA. Could this be the same misunderstanding?

Dr. **Bowen**. I took a rather strong view on that statement, and our staff could not remember having said those exact words.

Senator **Hawkins**. I bet.

Dr. **Bowen**. But, at the same time, it occurred at a time when there was some concern about the resources necessary to make those frequent detailed reports on that particular study. And I think it was in the heat of that concern that that remark or a similar one may have been made. We had no documentation of that.

Senator **Hawkins**. But you would not say that that attitude is typical of physicians administering to cancer patients at M. D. Anderson?

Dr. **LeMaistre**. Madam Chairman, of course not.

Senator **Hawkins**. What steps have you taken to insure the patients treated at your clinic that that kind of disregard for Federal regulations is not typical of your staff? Just the explanation you have given us, Dr. Bowen?

Dr. **Bowen**. In my capacity as administrative assistant for institutional overview of investigational drug research, I would say that that is certainly not a typical attitude at our institution.

Dr. **LeMaistre**. Madam Chairman, the steps that are being taken are recorded as those taken after the MTHHF incident. The question relates to an incident that is unrelated to it, but the sequence is rather parallel. The contact has been directly with individuals as to what will and will not be done by the institution. At the time of MTHHF incident, I asked that all such contacts from the NCI come through my office, and they have continued to come through my office since that point in time. So, we are aware of these and can speak for the institution, not an individual.

We have 5,000 employees of the University of Texas M. D. Anderson Hospital, well over 200 doctors. They are, like all of us, people with individual views about compliance with anything. As a consequence, an individual expression is not institutional policy. I believe had we had very clear understanding throughout all of the past years of a centralization of point of contact with a responsible institutional official, many of these things would have been clarified much more rapidly.

I commend that particular step because it is working in our institution and it has worked since June of this present year.

Senator **Hawkins**. In the followup to the July 13 site visit, the officials of NCI noted in their report that "There does appear to be a more general problem regarding protocols used for carrying out the clinical pharmacology studies under the M. D. Anderson contract". They concluded that these studies were not sufficiently clear and organized in the past. Have you taken special steps to improve your organization?

Dr. **Bowen**. Yes, may I respond to that, Madam Chairman?

Senator **Hawkins**. Yes, Dr. Bowen.

Dr. **Bowen**. We have taken a number of steps. As a matter of fact, in a series of steps which are still ongoing, we have a continuing review in our institution, of all of our procedures and policies.

In discovering with the MTHHF incident that there were situations which could inadvertently occur outside, not only extramural regulations but also our own institutional rules and procedures, we did an intense, and are still doing an intense review of all of our procedures and have put in a number of modifications of those procedures which we have described briefly at least in our written testimony which we have submitted.

For one thing, we have created a central office for research protocols which has the responsibility for insuring that not only institutional compliance is true of all protocols but also compliance with all NCI, FDA, and State regulations. We have documented each of our procedures in our one, two, three, four step-wise fashion. And we are seeing to it and documenting that every clinical investigator, both staff and fellow, receive these documents, read them, and understand them. In addition to which we have begun a broad educational program of our staff with regard to the institutional review process for compliance with all institutional and extramural rules and procedures.

A traditional and very effective mechanism for educating ourselves on any subject, particularly those which are medical or clinical investigation related subjects, is the grand rounds. The grand rounds is a program in which all of our staff come together at one time for sharing and instruction on a particular clinical or scientific subject by experts who are involved and who are knowledgeable.

We have already initiated through Dr. van Eys' work a major grand rounds on the institutional review process and on how protocols and other research activities are to be carried through our institution prior to their implementation and will be developing over the next few months a similar grand rounds program addressed specifically to the question of informed consent.

So, there are just a few of the examples of the fail-safes that we have put in, the procedures that we have clarified, and the check points that we have established to make sure that another incident like the MTHHF incident does not occur.

Senator HAWKINS. All of this happened after the outside monitors pointed out the deficiencies?

Dr. BOWEN. No, I do not think that it would be fair to say that all of this has happened. Obviously, and in all candor, we have intensified this effort to make sure that all safeguards are in——

Senator HAWKINS. Internally?

Dr. BOWEN [continuing]. But, as we have pointed out before, this was a process which has been developing and evolving over the years. And our situation prior to the MTHHF incident was, I think, significantly better than it was 5 years prior to that. The MTHHF incident, though, did illuminate some areas where there is a possibility for inadvertent circumnavigation of our institutional rules. And we have stepped in intensively to make sure that that cannot occur.

Senator HAWKINS. The four problems that we have discussed, the inadequate and outdated consent forms, the absence of information regarding side-effects, and four examples of protocol deficiencies are not what I would call isolated incidents. But you are telling me now that you have established an internal system and operation that would have disclosed these deficiencies. You now have that in place. At that time of the site visit you did not?

Dr. BOWEN. Part of those are in place, and others are in the process of going into place now.

Dr. LEMAISTRE. They are all going into place. Madam Chairman, let me be very specific. The point you raised in Dr. Shepard's memorandum dealing with clinical pharmacology studies was not corrected at the time. That has subsequently been corrected. All pharmacology studies require the same review as phase I drug applications. That corrects that problem, in our view.

I might point out that there is also another incidental fact that is needed; it may seem unrelated. But the NCI did review all of the drugs supplied in the past 6 years to our institution and found no other instances of testing without IRB or—and FDA approval.

That point, I think, needs to be entered into the record because I do not believe it has been said.

The specific points you address, however, deal with the institutional review procedure. I would like for Dr. van Eys, if he will, to speak specifically to those latter points that you have spoken to.

Dr. VAN EYS. The institutional review board, as it relates to the pharmacology studies, had already insisted that a separate informed consent be given for pure pharmacology studies from those of the phase I trial, in the sense that we thought it might be coercive to have this lumped together in one process. A patient might want to be a subject for the trial of the drug and refuse the pharmacology study, and that that would be appropriate.

That antedated the incident that you mentioned.

In addition, there is a very strict control over the dispensing of the drug through our pharmacy so that they cannot be ordered unless the protocol under which they are ordered are identified and that that in fact has been approved by the IRB. The IRB notifies the pharmacy whether a protocol has been approved or not, and it cannot be dispensed beforehand.

Senator **Hawkins**. I want to thank you gentlemen for coming today. It is refreshing to hear your testimony in describing the weaknesses and corrective measures taken. It is an example for all agencies, all departments that have been here prior to you, and all hospitals and centers that are looking to you for leadership. You really have measured up to that.

Dr. **LeMaistre**. Senator Hawkins, may I express on the part of my colleagues our gratitude for the opportunity to appear.

I did notice when I mentioned 15,500 patients receiving chemotherapy that you appeared to be surprised. Perhaps I should point out for the record, however, that only 186 of those in a 23-month period were entered into phase I studies. And I do know that, from previous testimony, you are interested in the toxic events associated with death. Our record shows that only four, about 2.1 percent, of the deaths that occurred had any evidence of toxicity associated with this.

I think that many times we fail to recognize that it is a risk in this particular situation that physicians feel is worth taking. And I am sure you agree with that point. We take much greater risks in some established procedures in cancer such as certain surgical procedures that are long established that have a much higher mortality rate than that.

So, I want to join again in your opening statement and that of Senator Kennedy in commending to the American public the way that the overall program is being handled and your recognition that it still can be perfected and we can do better. We thank you for it.

Senator **Hawkins**. I think each hearing we have brings about a lot of new measures to be placed, in the administration, at least, of this vital war on cancer. We appreciate your participation and recommendations.

Dr. **LeMaistre**. Thank you.

Senator **Hawkins**. The last panel will be Dr. Charles Moertel of the Mayo Clinic in Rochester, Minn. Dr. Moertel serves as chairman of the Committee on Community Oncology and Technology Transfer, a study commission established at my request by Secretary Schweiker.

Dr. Moertel, we certainly appreciate your patience in waiting so long to testify today and also your understanding.

The Commission that you head up was set up to address the problem of the transfer of cancer technology to community hospitals and physicians where most patients are treated at the local level in their own hometown. At our May 21 hearing, the subcommittee discovered a serious weakness in the dissemination of information regarding the latest cancer cure and treatment, and this transfer of information is vital to our national war on cancer. It has been targeted specifically by the Congress as an area that urgently needs improvement.

I appreciate your coming here today and bringing us up to date on the Commission's effort.

What have been the specific activities of the Commission since our hearing last May?

STATEMENT OF CHARLES MOERTEL, M.D., DIRECTOR, THE MAYO COMPREHENSIVE CANCER CENTER

Dr. MOERTEL. Thank you, Madam Chairman. I compliment you on your perseverence through a very long morning here. I will try not to be too garrulous.

As you are well aware, and certainly you have recently highlighted in these hearings, the National Cancer Act specifically mandates that the technology of new and hopeful cancer management be expeditiously transferred from the academic centers where they are developed to the community centers where over 80 percent of cancer patients are diagnosed and treated. I think both House and Senate reports accompanying the 1974 amendments to the act left no room for doubt as to the intent of Congress. It was specifically stated that no American cancer patient should be deprived of highest quality cancer care simply because of where he lives.

In my opinion, Senator Hawkins, in the past we have not adequately responded to this very clear charge.

When Dr. DeVita took the office of director, I know that the correction of this deficiency was one of his highest priority objectives. This is one of the reasons why I was personally so very pleased with his appointment. To meet this objective, he established a committee within his division of resources, centers, and community activities. With the impetus provided by your hearings, this committee has now been made directly responsible to Dr. DeVita.

I accepted the chairmanship with enthusiasm. I was fortunate, I think, to bring to this committee the people who I consider to be the most capable in this country to deal with the problem. We have representation of all concerned cancer physician disciplines as well as cancer nursing. We have strong representation of academic centers and strong representation of the community.

These people of diverse interests, I feel, have been able to set aside parochialism and develop and unanimously approve a program which is in the interests of the American people.

Time will only permit me to present in summary, but I hope you will be able to read the full documentation of this program since I feel it is highly pertinent to the responsibilities of your committee.

[Material referred to follows:]

Mayo Clinic
Rochester, Minnesota 55901 Telephone 507 284-2511

Comprehensive Cancer Center

1981 NOV -2 AM 9 19

October 28, 1981

Senator Paula Hawkins
Room 1327
Dirksen Senate Office Building
Washington, D.C. 20510

Dear Senator Hawkins:

Knowing your interest in the progress we have made on developing programs for community cancer centers and cancer technology transfer, I am enclosing a draft of this program as designed by our committee and as recently approved by the Board of Scientific Counselors of the Division of Resources Centers and Community Activities, NCI. As you know, Mr. Mischke has invited me to testify briefly before your Committee regarding this program and also to submit this draft for inclusion in the records of your hearings. I thought you might wish to review this before the hearings. I would be very happy to answer any questions you may have regarding it. I hope you will find it to be a program of merit that is responsive to the need brought out by your Committee. I wish to thank you and your Committee for the strong encouragement you have provided for the evolution of this program.

Sincerely yours,

Charles G. Moertel, M. D.

CGM:mab

Enclosure

COMMUNITY CLINICAL ONCOLOGY PROGRAM

I. Introduction

This community clinical oncology program is designed to meet a clear responsibility of the National Cancer Program mandated by Congress and enunciated in both Senate and House reports accompanying the 1974 Amendments to the National Cancer Act: That no American cancer patient should be deprived of highest quality cancer care simply because of where he lives. This program is also designed to facilitate technology transfer and to conduct significant clinical cancer treatment and prevention research that will have direct pertinence to the overwhelming majority of cancer patients who are managed in the community. If these goals can be met a major step will have been taken towards primary objectives of cancer control, i.e. a reduction in the morbidity and mortality of cancer. This program is also based on the conviction that by mobilizing the resources of the community, the research objectives of the National Cancer Institute will not be compromised but rather will be complimented and made more cost effective.

II. Goals

This program has the following specific objectives.

a. To bring the highest quality cancer care to the American community.

b. To bring the resources of the community hospitals and clinics into national clinical cancer research programs.

c. To develop and improve methods for transfer of cancer management technology from academic center to community clinic and hospital.

d. To bring the resources of the community clinics and hospitals into national cancer control research programs and to conduct cancer control research at the community level

III. Background and Justification

A. To bring the highest quality cancer care to the American community

Over 80% of all cancer patients in this country have all cancer care administered in the community and a substantial proportion of the remainder have most of their care administered in the community. The cost of travel and lodging required for care at major cancer centers may be prohibitive for many patients who live at distances from such centers. Even those who could afford to travel to distant centers understandably prefer to remain at home close to family and friends when they are dealing with a fatal or potentially fatal illness. Facilitating delivery of high quality cancer care to those cancer patients who remain in their communities is a clear responsibility of the National Cancer Program.

National end result statistics show that over 50% of all cancer patients will not be cured by standard treatment approaches currently available. The only realistic hope for these patients is offered through entry on clinical research programs. Patients treated in the community have an equal right to such hope as those treated in university centers.

B. To bring the resources of the community hospitals and clinics into national clinical cancer research programs.

As a product of the National Cancer Program a great many physicians specializing in the treatment of malignant disease have been trained and have established practices in the community. Consequently increased numbers of cancer patients have the convenience and economy of obtaining high quality care in their home area. As an adverse effect of this accomplishment, however, many major cancer centers have found that patient availability for entry into their clinical research programs has been significantly curtailed. This has seemed to be particularly true for patients with early stage disease. It must also be recognized that results of clinical research programs confined only to that select group of patients treated at major cancer centers are not necessarily representative of the results of such a program applied at the community level where most cancer patients are treated.

With the establishment of medical oncology as a subspecialty, a large number of medical oncologists have received their subspecialty education at major academic cancer centers and for almost all this training has included experience in clinical research. Similarly there are now well trained therapeutic radiologists working with excellent equipment in most large and medium sized communities. There are, therefore, highly qualified professionals in the community fully capable of carrying out clinical research. Experience within several groups (ECOG, NCOG, NCCTG, NSABP) has clearly indicated that high quality clinical research data can be produced by cancer physicians in community practice. There is also evidence that involvement of the private sector of cancer practice into national clinical research programs may substantially reduce the cost of such programs. There is therefore justification for the belief that integrating the assets of academic cancer centers and community cancer centers for the purpose of conducting clinical cancer research will not only provide adequate patient material to meet the needs of national programs but will also meet this need with high quality data and with enhanced cost effectiveness.

C. To develop and improve methods for transfer of cancer management technology from academic center to community clinic and hospital

The expeditious transfer of new and improved technology in cancer management from academic centers to the patient in the community is an explicit goal of the National Cancer Program. Such technology transfer is also an indispensible foundation stone for cancer control on a regional or national level. Technology transfer in cancer management today is frequently imperfect because of delayed communication, casual attention to detail and quality of transfer procedures, little or no expert guidance and quality control as the new technologies are applied at the community level, and a frequent total lack of evaluation of short term and long term impact of the new technologies on the cancer patients in the community. These defects in our technology transfer process may result in inordinant delays in bringing new technologies of value to the community where the great majority of cancer patients are managed or in imperfect applications of new technologies at the community level. Current defects in quality control and evaluation of technology transfer may also result either in unfair discrediting of new technologies because of improper application or in perpetuation of technologies that in fact have no substantive value when applied at the community level.

A major purpose of this program is to provide prompt transfer of hopeful new technologies in cancer management to the patient in the community by promotion of interaction between academic center and community physician in a working relationship and in a clinical research mode. This technology transfer will be accomplished in a manner that will allow for concurrent quality monitoring and evaluation of impact under controlled conditions within the community. It is also hoped that this program will stimulate the development, application, and evaluation of innovative approaches in technology transfer tailored to specific community or regional needs.

D. To bring the resources of the community clinics and hospitals into national cancer control research programs and to conduct cancer control research at the community level.

Certainly any program dealing with the broad objectives of cancer control, i.e. to reduce incidence, morbidity, and mortality of cancer, must be directly concerned with the cancer patient in the community since this is where the overwhelming majority of cancer patients are when they develop their cancer, are treated for their cancer, and die of their cancer. Many cancer control programs in the past have suffered from a failure to directly involve the community cancer physician in planning and conduct of interventions or evaluations. Of equal importance is the great difficulty in achieving uniform and high quality data in any cancer control study involving defined large populations.

It would be the intent of this program to establish for cancer control studies the same complimentary interaction of university cancer center and community cancer center as would be established for studies in cancer treatment and prevention. Standardization of pathology interpretation and surgical reporting, quality control of radiation therapy delivery, uniform reporting of medical treatment interventions, and systems of data logistics and data quality control all would have equal application to cancer control research as to the usual treatment and prevention research. The simple attainment of uniform and high quality cancer data would provide a foundation for cancer control research that has never been attained before. Also the devoted involvement of the community physician would provide an invaluable asset. In addition, for many cancer control objectives pertaining to symptomatic and supportive care, the hospice concept, and psychosocial aspects of cancer, the community cancer physician may be the most motivated and most capable to carry on research programs.

Admittedly cancer control research is in a much more developmental stage than cancer treatment research, but involvement of the community cancer center would seem even more vital to the successful attainment of cancer control objectives. It is the clear intent of this program to stimulate participation by community cancer centers in national cancer control programs and in their evaluation. Participants in the program will be expected to set priority goals for cancer control and to define methods of achieving these goals. A specific early high priority goal would be to achieve a standardization among research bases to permit ease of data utilization for cancer control purposes.

It is not the purpose of this program to subsidize private cancer practice or to subsidize the conduct of non-research "protocols" for best standard clinical practice. The conduct of best clinical practice should be regarded as the primary responsibility of the physician in private practice. Certainly, however, education and technology transfer will be a vital cancer control objective of this program. Also, it may be anticipated that participation of community centers in well designed and conducted clinical research protocols will enhance the overall quality of care rendered by the community center. It is specifically not the purpose of this program to provide funding for every private physician who treats cancer patients regardless of his research motivations or capabilities. This is a research program that will be organized for the primary purpose of providing the highest quality research performed at the lowest possible cost.

This program is also not intended to replace existent and successful organizations involving cancer centers, cooperative groups, and community centers. This program should facilitate and enhance such successful endeavors. It is clearly not the purpose of this program to regiment all community clinical oncology research organizations into a common mold. Innovative approaches are encouraged.

It is projected that this overall program will eventually involve between 100 and 200 community clinical oncology programs (CCOP) demographically and geographically located so that they can conveniently serve the entire population of the United States. The program will continue to involve a still greater number of private cancer physicians and surgeons and smaller clinics in the traditional satellite relationships with major cancer centers, regional cooperative groups, and national cooperative groups. It is anticipated that Community Clinical Oncology Programs funded under this program will work in cooperation with approximately 20 new or existent research bases such as major cancer centers, national cooperative groups, or regional cooperative groups. It is hoped that this program will bring a minimum of 10,000 cancer patients as required by nationally approved clinical cancer research protocols.

IV. Organization of Community Clinical Oncology Programs

Since this program will have major objectives pertaining to both the Division of Cancer Treatment and the Division of Resources, Centers, and Community Activities, it is anticipated that these divisions will work together in coordinating strategies, funding resources, and peer review mechanisms. This coordination will be essential both for integrating community cancer centers into existing groups as well as for the formation of new groups.

The fundamental organization of this program will be a research base (national cooperative group, regional group, contract supported group or major cancer center) that relates to a number of Community Clinical Oncology Programs or to individual cancer physicians or to smaller clinics or consortiums. The affiliation of a Community Clinical Oncology Program with a research base will be a joint decision. In these decisions consideration would be given to demographic and geographic relationships, feasibility of quality control procedures, and the need of an existing research base for an influx of additional patient numbers.

The research base would have a number of vital functions in this program including those provided by an operations office and statistical center and, particularly, the development of research strategies and procedures in early stage that will later be evaluated in larger studies conducted by the group as a whole. Adequate funding must be provided to the research base to meet these responsibilities to the community clinic participants.

A primary responsibility of the Community Clinical Oncology Program would be the entry of patients on national protocols conducted through their research group and also to participate with the research base in programs of cancer control. It would also be expected that the individual Community Clinical Oncology Programs would have equal voice to that of other individual member institutions in the administration and scientific affairs of the research base. Adequate funding would be provided for these activities either individually for the larger and established community centers or under consortium agreement for smaller or developing centers.

When this program is fully implemented it is anticipated that National Cancer Institute distribution of investigational drugs, including Category C agents, would be restricted to participants in this program and in other clearly defined National Cancer Institute research programs.

It would not be the purpose of this program to dictate specific treatment, prevention, or control research objectives and projects. These projects would be conceived and planned by the participating Community Clinical Oncology Programs and their research bases and presented for appropriate peer review.

V. Community Clinical Oncology Program (CCOP)

A. A Community Clinical Oncology Program (CCOP) may be defined as a single clinic, a group of practicing physicians, a single hospital, or a consortium of physicians and/or clinics and/or hospitals. In the latter instance cohesion must be demonstrated and there must be a unifying administrative structure. The consortium approach is particularly encouraged when several community cancer centers are serving the same population area.

B. Each funded Community Clinical Oncology Program must have a designated and committed multidisciplinary professional team including surgeons, radiation oncologists, medical oncologists, pathologists, and oncology nurses. Appropriate other disciplines may be added e.g. gynecologic oncologists, pediatric oncologists. One of this group will serve as principal investigator and a representative of each of the remaining subspecialties will serve as coinvestigators. An associate principal investigator will also be named to assure continuity in the event of departure of the principal investigator.

C. Each Community Clinical Oncology Program must have a well defined area for administrative activities which will serve as a focus for data management, quality control, and communication. Usually this would be in a hospital or clinic and staffed by a designated administrative person. It is anticipated that this area will be in close proximity to clinical activities so that prompt data transmission can be accomplished as well as on scene eligibility checks and quality control.

D. Each Community Clinic Oncology Program must have evidence that an affiliation has been established with a nationally recognized clinical cancer research base, e.g. major cancer center, national or regional cooperative group. Multiple affiliations are discouraged unless they are clearly not conflicting, e.g. ECOG for adult tumors, CCSG for childhood tumors.

E. Each Community Clinical Oncology Program must identify and characterize its patient service area. Emphasis will be placed on demographic and geographic distribution of community centers. Multiple Community Clinical Oncology Programs competing for the same patient population will not be approved. Consortiums of hospitals, physicians, or clinics serving the same population are encouraged.

F. Each Community Clinical Oncology Program must have a demonstrated potential and stated commitment to contribute at least 50 patients per year to approved clinical research protocols active in the center or group with which the community center is affiliated, to protocols of other nonconflicting groups, or to overall national protocols e.g. for rare tumors. To meet the general goals of the program it would be anticipated that less than 12 percent of patients presenting with any given malignant disease problem would be required as protocol entries to meet program needs.

G. Each Community Clinical Oncology Program is encouraged to have well planned procedures for regular communication with the practicing physicians of their region, e.g. education programs, workshops, grand rounds, tumor boards, etc. These can be conducted either independently or in cooperation with the major center or group with which the community center is affiliated.

H. Each Community Clinical Oncology Program is encouraged to have well planned programs to meet the human needs of cancer patients.

in their community, e.g. patient education, cancer rehabilitation, "hospice" programs, etc. Again these may be either independent or in cooperation with the major center or group with which the community center is affiliated.

I. Each Community Clinical Oncology Program must have, either individually or in cooperation with a major center or national group, a plan for evaluating the impact of its community programs.

J. Funding for a Community Clinical Oncology Program will be based on established ability to contribute patients to national clinical research protocols and the ability to conduct the required cancer control and evaluation activities. Funds will be available for more extensive cancer control type activities or for evaluation activities if such funding can be justified before peer review. Anticipated total yearly treatment research budget for a center contributing the minimum of 50 patients and without supplemental cancer control activities would be $50,000. The anticipated indirect cost would be minimal. The budget would be increased proportionately for centers capable of greater case contributions. Allowable items in the budget would be for personnel engaged in data handling and study assistants, supplies and services directly related to study activities (e.g. processing and sending material for pathology review, processing and sending port films for radiation therapy quality control), travel to meetings directly related to study activities, and support for cancer control activities. Physician compensation would be allowable only for time spent on the project other than clinical care and this time should be documented. Total funding as well as allowable physician compensation would be increased proportionately for additional peer review approved cancer control activities. Funding would be allowed for five years. Developmental grants for up to a two year period could be allowed for community cancer centers with a clearly established potential for case contribution that had not been documented by past performance. These grants could be extended for an additional three years by NCI staff review without site visit if adequate case contributions could be documented during the initial two years.

VI. Research Bases for Community Clinical Oncology Program Activities

A. It is anticipated that the research bases for Community Clinical Oncology Program activities would be provided through comprehensive cancer centers, other university cancer centers, national cooperative groups or regional cooperative groups. It is hoped that the need of this program can be met by existing research bases currently funded by the Division of Cancer Treatment or those to be funded under the current regional group RFA. If this does not prove to be the case funding would be provided for the establishment of additional research bases specifically oriented to this program.

B. The general function of a research base would be to stimulate, facilitate, coordinate, and evaluate the research and control activities of its associated Community Clinical Oncology Programs and other community affiliates.

C. The research base would have defined mechanisms for the community participants to have direct input to the administration and policy decisions of the respective research bases. It would be anticipated that approved and funded Community Clinical Oncology Programs would be voting research base members. It is also anticipated that community clinic members would have appropriate representation on governmental and operational committees of the research base.

D. Specific functions would include the following:

1. To assess the capabilities of community members and affiliates for participation in clinical research and cancer control activities.
2. To assist the community members and affiliates in any necessary upgrading of personnel and facilities and to provide training when indicated for supporting personnel, e.g. data handlers, study assistants, oncology nurses, etc.
3. To join with the community members and affiliates in developing and/or making available appropriate clinical research protocols.
4. To provide appropriate quality control procedures for data recording, protocol compliance, and reporting of adverse reactions.
5. To join with radiation therapists of the community members and affiliates by assisting with treatment planning and in providing quality control both with regard to standardization of equipment and to dose and field.
6. To join with surgeons in the community members and affiliates to standardize operative reporting and, when feasible, operative procedures.
7. To join with pathologists of the community members and affiliates to standardize pathology reporting, to standardize pathology procedure, and in providing mechanisms for pathology review for appropriate protocols.

8. To provide an Operations Office which will provide regular and timely pertinent communication with affiliated community members and affiliates and establish logistics for data transmission.
9. To provide a Statistical Center for data management and to provide statistical assistance in the protocol design, protocol monitoring, data analysis, and manuscript preparation.
10. To monitor new drug procurement, to transmit new drug orders, and to monitor new drug use by affiliated community clinic members.
11. To organize regular meetings with its community members and affiliates for review of ongoing research activities, planning of future activities, and related professional education.
12. To join with its community members and affiliates in the planning and conduct of cancer control activities.
13. To assist community members and affiliates in evaluating the impact of their research and control activities.
14. To evaluate the quality of performance and its affiliated community members and affiliates. This evaluation will specifically include monitoring of patient accrual to research protocols.
15. To prepare at least once annually a comprehensive report of overall Community Clinical Oncology Programs.

E. For funding under this program it is anticipated that an existent or new research base will be affiliated with at least eight Community Clinical Oncology Programs or their equivalent in smaller community units contributing at least 500 research protocol entries per annum.

F. It is anticipated that a research base meeting the minimum requirement as described in D would be funded for their activities in this program at a total cost of $150,000 per annum. Proportionately greater funding would be allowed for a larger number of community protocol entries. Additional funds could be provided for appropriate and approved cancer control activities. Additional funds could also be added for subcontracting the activities of "satellite" community oncologists and clinics who do not have sufficient case entry potential to justify independent funding as a Community Clinical Oncology Program.

G. Allowable budget items for a research base would include professional (physician, statistician, nurse) staff salaries for administrative and advisory activities; paraprofessional salaries for administrators, data clerks, statistical assistants, secretaries; supplies, services, and equipment directly related to support services; computer charges; editorial, graphic, and photographic services; travel.

H. Awards would be made for five years for established groups. Developmental awards of two years could be made for groups with demonstrable potential but without established community productivity. These latter awards could be extended for an additional three years by NCI staff review if productivity is established during the initial two years.

VII. Review Procedures

A. It is anticipated that individual research bases and affiliated Community Clinical Oncology Programs would be evaluated at a single site visit.

B. Awards would be based on approval and priority scores of the group as a whole (research base plus affiliated community centers). Each Community Clinical Oncology Program would also be individually judged for approval and priority.

C. Three categories of funds would be awarded.

1. Funding for operation of the research base e.g. statistical center, operations office.
2. Funding for smaller community clinics and individual physician participants awarded to the research base to be distributed by consortium agreement. This funding arrangement would also seem most appropriate for developing groups.
3. Direct awards to approved Community Clinical Oncology Programs.

D. Supplemental awards could be sought by each group for addition of new community participants or based on increased productivity of the community participants. NCI staff would decide whether site vitis was required for approval of such supplements.

E. If an institution providing a research base will also be entering patients into protocols of the group it supports, or if some protocol patients will be jointly managed by the supporting institution and the community centers, this supporting institution may also request additional funding for its protocol patient contributions. These funds will be awarded at a rate not to exceed that awarded to the community clinic participants unless special services are offered to protocol patients for which additional funds can be justified, e.g. special laboratory procedures.

Mr. **Moertel**. At present, I feel that the transfer of cancer management technology from the research center to the practicing physician is frequently very poorly accomplished. There may be great delays, only casual attention to detail and quality of the transfer procedure, little or no expert guidance as the new technologies are applied at the community level, and usually no evaluation of the real impact of the new technologies on the cancer patient in the community.

All of these deficiencies can have a very destructive effect. New technology of real value can be unfairly discredited because of improper application or, perhaps even worse, a technology of no substantive value can be perpetuated because no one ever really evaluated its impact on the community.

This new program is specifically designed to provide prompt transfer of hopeful technologies by providing a working relationship between academic center and community physician in a clinical research mode so that the impact can be evaluated.

Our emphasis has been placed on demographic and geographic distribution of participants so that the needs of the entire Nation can be served.

In this program there will be a number of research bases. They will be distributed throughout the country and provided by comprehensive cancer centers or national or regional cooperative groups. Each of these research bases will in turn have responsibility for interacting with a defined group of community cancer centers. These community cancer centers will then reach out to practicing physicians of their respective regions, and they will also be encouraged to have well-planned programs to meet the human needs of cancer patients in the community.

In these efforts they will have the direct working cooperation of pertinent experts from academic centers. The academic centers will join with the community participants in the planning and conduct of research and cancer control protocols. And they will also join in providing appropriate quality control procedures for the conduct of these protocols. They will assist community participants in evaluating the impact of these interventions on their respective communities, and in cooperation with the National Cancer Institute procedures will be developed to monitor new drug procurement, to monitor new drug use, and to insure prompt reporting of adverse drug reactions.

Can such a program really work? Is it feasible? Yes, it can. Yes, it is. And I know that because we have done it.

Across the northern tier of the United States there is no major cancer center between our institution, which is next to the Mississippi River on the east and beyond the Rocky Mountains far to the west. Although there are a lot of cancer patients out there, this area had really been completely neglected by the national cancer program.

A few years ago, with Dr. DeVita's assistance, we joined together with the community clinics in that region. We went out to them. We worked with their surgeons, their radiation therapists, their medical oncologists, their pathologists. We assisted them in recruiting any needed personnel. We helped train their cancer nurses, their data handlers. And at the present time I think some of the most meaningful clinical cancer research in this country is being carried out by these community cancer centers. The quality of their work is outstanding, and it is remarkably cost-effective.

One of the most important things that we at the Mayo Clinic have learned from this experience is that cancer technology transfer is a two-way street. The community physician works day by day with the patient and his family. They are very conscious of the impact of treatment procedures on the quality of life for the cancer patient. And they have taught us.

They are also very aware of the importance of cost containment and health care delivery, something that I think is easy to forget when you are practicing in an academic center. They are highly motivated to meet the human needs of their cancer patients. And they are now taking the lead in developing such programs for our group.

You will see in the program before you that there is the insistence that the community physician be given voice and a voice that will be heard.

This will be a costly program over the next 5 years, probably some $60 million. If wisely spent, it can be one of the most highly productive investments of the entire national cancer program. But I must emphasize to you, however, the importance of integration and coordination of this program. If it simply involves giving a pot of money to academic centers, going off in one direction, and giving another pot of money to private doctors going off in another direction, with a vague promise that somehow they are going to get together, then I feel this program will be a $60 million boondoggle. And there is considerable pressure from both sides to do just that.

The keystone of this program, however, is a demonstrated, tangible commitment to productive interaction of center and community physician. Funding is allowed only for and is contingent upon this type of interaction. Dr. DeVita has wisely, I feel, charged our committee to continue to function assisting and monitoring the implementation and conduct of this program.

I am considered by some as a bit of a maverick, Senator. I can assure you that, if this program does not function as it has been approved and as I have represented it to you today, I am going to be right back here knocking on your door asking to testify again.

Senator, I hope you agree that what you have before you is a fine program representing the efforts of many dedicated people that can produce real and visible benefit for the American cancer patient both today and tomorrow.

I personally wish to thank you for catalyzing this program.

[The prepared statement of Mr. Moertel follows:]

STATEMENT OF DR. CHARLES MOERTEL

Senator Hawkins, as you are well aware and have recently highlighted in these hearings the National Cancer Act specifically mandates that the technology of new and hopeful cancer management be expeditiously transferred from academic centers where they are developed to the community where over 80 percent of cancer patients are diagnosed and treated. Both House and Senate reports accompanying the 1974 amendments to the act left no room for doubt as to the intent of Congress. It was specifically stated that no American cancer patient should be deprived of highest quality cancer care simply because of where he lives. It is my opinion Senator Hawkins that in the past we have not adequately responded to this clear charge. When Dr. DeVita took the office of Director, I know that correction of this deficiency was one of his highest priority objectives. This is one of the reasons why I was so personally pleased with his appointment. To meet this objective he established a committee within his Division of Resources, Centers and Community Activities. With the impetus provided by your hearings this committee has now been made directly responsible to Dr. DeVita. I accepted the chairmanship with considerable enthusiasm and I was fortunate to be able to bring to this committee the people who I considered the most capable in this country to deal with the problem. We have representation of all concerned cancer physician specialties as well as cancer nursing. We have strong representation of academic centers and strong representation of the community. These people of diverse interests, I feel, have been able to set aside parochialism and develop and unanimously approve a program which is in the interest of the American cancer patient. Time will only permit me to present in summary, but I hope you will be able to read the full documentation of this program since I feel it is highly pertinent to the responsibilities of your committee.

At present I feel the transfer of cancer management technology from research center to the practicing physician is frequently poorly accomplished. There may be great delays, only casual attention to detail and quality of transfer procedures, little or no expert guidance as the new technologies are applied at the community level, and usually no evaluation of the real impact of new technologies on the cancer patient in the community. All of these deficiencies can have a very destructive effect. New technology of real value can be unfairly discredited because of improper application or, perhaps even worse, a technology of no substantive value can be perpetuated because no one ever really evaluated its impact on the community.

This new program is specifically designed to provide prompt transfer of hopeful technologies by promoting a working relationship between academic center and community physician in a clinical research mode so that impact can be evaluated. Emphasis will be placed on the demographic geographic distribution of the particpants so that the needs of the entire nation may be served. In this program there will be a number of research bases. They will be distributed throughout the country and provided by comprehensive cancer centers or by national or regional cooperative groups. Each of these research bases will in turn have responsibility for interacting with a defined group of community cancer centers. These community cancer centers will then reach out to the practicing physicians of their respective regions and they will also be encouraged to have well planned programs to meet the human needs of cancer patients in their community. In these efforts they'll have the direct working cooperation of pertinent experts from the academic centers. The academic centers will join with the community participants in the planning and conduct of clinical research and cancer control protocols and in providing appropriate quality control procedures for the conduct of these protocols. They will also assist the community participants in evaluating the impact of these interventions on their respective communities. In cooperation with the National Cancer Institute procedures will be developed to monitor new drug procurement, to monitor new drug use, and to insure prompt reporting of adverse drug reactions. Can such a program really work? Is it feasible? Yes it can. Yes it is. And I know that because we have done it. Across the northern tier of the United States there is no major cancer center between our institution next to the Mississippi and beyond the Rocky Mountains to the West. Although there are a lot of cancer patients out there, this area had really been completely neglected by the National Cancer Program. A few years ago with Dr. DeVita's assistance we joined together with the community clinics in that region. We went out to them and worked with their surgeons, their radiation therapists, medical oncologists, pathologists. We assisted them in recruiting any needed personnel. We helped train their cancer nurses, their data handlers. At the present time I think some of the most meaningful clinical cancer research conducted in this country is being carried out by these community clinics. The quality of their work is outstanding and it is remarkably cost effective. One of the most important things that we at the Mayo Clinic have learned from this experience is that cancer technology transfer is a two way street. The community physicians work day by day with the patient and his family. They are very conscious of the impact of treatment procedures on quality of life for the cancer patient and they have taught us about this. They are very aware of the importance of cost containment in health care delivery, something easy to forget when you are practicing in an academic center. They are highly motivated to meet the human needs of their cancer patients and they are now taking the lead in developing such programs for our group. You will see that in the program before you there is the insistence that the community physician be given voice and a voice that will be heard.

This will be a costly program. Over the next five years some $60,000,000. If wisely spent, it could be one of the most highly productive investments of the entire National Cancer Program. I must emphasize to you, however, the importance of integration and coordination of this program. If it simply involves giving a pot of money to the academic centers, going off in one direction, and giving another pot of money to private doctors, going off in another direction, with the vague promise that somehow they are going to get together—then I feel this program will be a $60,000,000 boondoggle, and there is considerable pressure from both sides to do just that. The keystone of this program, however, is demonstrated tangible commitment to productive interaction of center and community physician. Funding is only allowed for and is contingent upon this type of interaction. Dr. DeVita has wisely, I feel, charged our committee to continue to function, assisting and monitoring the implimentation and conduct of this program. I am considered by some as a bit of a maverick, Senator, and I can assure you that if this program does not function as it has been approved and as I have represented it to you today, I am going to be right back here knocking on your door asking to testify again. Senators, I hope you will agree that what you have before you is a fine program representing the efforts of many dedicated people that can produce real and visible benefit for the American cancer patient both now and tomorrow. I personally wish to thank you for catalyzing the development of this program.

Senator **Hawkins**. Thank you, doctor. What facilities are available to the community physicians that were not available 6 months ago?

Dr. **Moertel**. I think very little that I can identify at this point in time, Senator, because this program has just passed the Board of Scientific Counselors of the Division of Resources, Centers and Community Activities. It is now moving up to the National Cancer Advisory Board for their approval. RFAs have to be worked out.

So, at the present time this is a concept that I hope will come to fruition.

In our own region, where we have had a model program of this kind going on for 5 years, there are a great deal of facilities.

Senator **Hawkins**. What is your timetable for the new program?

Dr. **Moertel**. I hope it is going to be very rapid, Senator. I feel a strong need for the community centers now. I think you feel a strong need for the community centers now.

I really can see very little reason for delay in implementation of this program. There have been far more complex programs that have been brought to fruition in very short periods of time. I would be most unhappy if this drags on for 6 months, 1 year, 2 years with the hope that perhaps it will go away. I think it should be implemented now, Senator.

Senator **Hawkins**. We join you in that expectation.

You appear to have great hopes for the community clinical oncology program. What distinguishes this program from its predecessors, the Community Oncology Program and the Community Hospital Oncology Program?

Dr. **Moertel**. The community oncology programs are really quite a different breed. These have not been programs to integrate the activities of the academic centers and the community centers in joint programs of research nature so that their impact can be evaluated. These have been primarily programs to build up within certain select communities the quality of cancer practice, the quality of cancer control. They have in essence been demonstration projects that have of necessity had to be very limited in the number of communities that were impacted.

This is going to be a far more extensive program that is designed to have its evaluation impacted. The model information derived from the previous community oncology programs will, hopefully, provide a background for many of the programs that might be instituted here.

Senator **Hawkins**. You mention in your report on the community clinical oncology program that it is hoped that this program will bring a minimum of 10,000 patients as required by nationally-approved clinical cancer protocols. Is there a shortage of patients for clinical protocol?

Dr. **Moertel**. I think in some instances there is, Senator. And the reason is because in many diseases we have had quite effective standard treatments. I say quite effective because none of them are all that effective. And many are associated with considerable risk. Many are associated with toxic reactions.

Few, although some are—but few chemotherapy programs are associated with cure, which I think must be our objective.

I feel that there is a tendency now for patients to be treated in the community with these partially effective treatments rather than to move forward into clinical research areas that would provide them with considerably more hope of improvement.

If we cut off this flow of patients into programs directed toward improvement, I am afraid we will be left with a rather intolerable stalemate in our battles against malignant disease. We are finding that some of our major cancer centers are no longer having the flow of patients to them that they had had in the past. This flow is being interrupted at the community and for very good reason; people would rather be treated at home. It is more comfortable to be treated at home. It is more economical to be treated at home.

But I think, if we can bring about this union of the community cancer center and the academic centers, there is no reason to sacrifice progress. You can allow the patient all the advantages of treatment in his home community without depriving him of the hope that can be provided by new directions in cancer research.

Senator **Hawkins**. We heard testimony last Tuesday of the tremendously high costs of cancer treatment. Is there any significant hope that these costs will be reduced during the foreseeable future?

Dr. **Moertel**. I wish I could say yes to that, Senator. I am afraid I have to say no. And I am afraid that I would predict that many of these costs will go in the opposite direction.

The truly significant advances in cancer treatment that I can predict over the years ahead, I am afraid, are going to involve far greater sophistication than those that we have used to date.

Senator **Hawkins**. Will they be available at the local level?

Dr. **Moertel**. Yes. But they will be available in special ways. For example, one of the new technologies we are using at the Mayo Clinic is intraoperative radiation therapy. Now, there are some very strong arguments to be made that this may be an exceedingly effective treatment for some types of malignant diseases. But it requires very sophisticated equipment, expensive equipment, expensive operating facilities. For this type of treatment we would hope that, if this is significantly effective, through our community network patients would be brought down to us for this expensive treatment episode, where our equipment could be cost-effective, but then quickly brought back to the community cancer center, where their sustained management will be carried out.

So, I would hope that through a network like this we can avoid some of the problems that we have got into in the past with things like CT scanners, for example, where they proliferated everywhere. If we can develop these types of community networks, we can have the sophisticated and the expensive in one center but a strong working relationship developed with the community so that the patient does not have to stay at the center forever but so you do not lose evaluation of impact. This is carried out through the community center in the data systems that are established with the academic center.

I think that we have got to look at cost-effectiveness because it is just absolutely essential. I think that community center working together with academic center is going to help considerably with cost-effectiveness. We see it now in research efforts. Within our north central cancer treatment group. The average charge over the last year per patient entry on our research protocol has been $300. The average charge in the national cooperative groups of academic centers is around $1,500. In some of the NCI contract groups it has gone up to $11,000 per case entry.

And there are reasons for this greater economy of clinical research at the community level. You bring in the private sector. You do not have other university functions that make up your overhead. Also you have a community doctor who looks at a test and says: "Well, that is awful nice but, goodness sake, it is too darn expensive, and it is not really going to make any difference in my patient's management anyway."

So, I think there is a potential for developing necessarily more expensive sophisticated cancer care in the years ahead but still maintaining overall economy in health care delivery by vigorously working to contain the containable costs.

Senator HAWKINS. Thank you so much, Dr. Moertel, for your contribution to our hearings. We would appreciate your keeping us apprised of the progress in transferring cancer treatment technology to the community level.

CLOSING STATEMENT

At the start of today's hearing I inquired "Who is to blame?" For the management deficiencies that have plagued the NCI for years.

I am afraid that the responsibility for these problems lies with the Congress.

Responsible oversight of these programs is the function of the Congress. It apparently has been so weak that the administrators of these agencies have not gotten the message that efficient management will be demanded—especially in a program that is intimately involved in the life and death of cancer patients. Confusion and disorganization must end. Patients must be adequately informed, life-threatening drug reactions must be promptly reported, clinical trials must be approved and monitored, effectively and adequately. NCI and the FDA have serious and damaging program deficiencies which have crippled these agencies and jeopardized patient safety.

The priorities are too urgent, the consequences too great for us in the Congress to ignore our responsibility of overseeing the functions of these agencies any longer.

Our inquiry into this matter will continue until we are convinced that the management of the National Cancer Institute is fully capable and willing to respond to program deficiencies. We must restore hope to the thousands of patients and their families who have been victimized by this dread disease.

I would like to reiterate my position that I remain committed to NCI's drug development program. It is a vital and necessary agent in the war against cancer. But if left unchecked it will become a harmful enemy. We must restore public confidence in NCI and FDA so that proper drug development programs can continue with proper leadership.

The people of this country will require no less from those of us in the Congress charged with the oversight of these programs. We, in turn, will require that same high standard of performance from these Government officials.

We will conclude these hearings at this time.

[Whereupon, at 1:30 p.m., the subcommittee was adjourned.]

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